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REVIEW ARTICLE

# The genetics of ductal adenocarcinoma of the pancreas in the year 2020: dramatic progress, but far to go

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## Abstract

The publication of the "Pan-Cancer Atlas" by the Pan-Cancer Analysis of Whole Genomes Consortium, a partnership formed by The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC), provides a wonderful opportunity to reflect on where we stand in our understanding of the genetics of pancreatic cancer, as well as on the opportunities to translate this understanding to patient care. From germline variants that predispose to the development of pancreatic cancer, to somatic mutations that are therapeutically targetable, genetics is now providing hope, where there once was no hope, for those diagnosed with pancreatic cancer.

## Introduction

Little more than a decade has passed since the exomes of a series of pancreatic cancers, by which we mean ductal adenocarcinomas, were first sequenced [1]. This decade saw an unimaginable explosion in knowledge of the genetic drivers of all types of cancer, culminating in a tour de force series of publications describing integrated analyses of 2658 cancers across 38 cancer types by the Pan-Cancer Analysis of Whole Genomes Consortium of The Cancer Genome Atlas and the International Cancer Genome Consortium [2–7]. These publications provided unprecedented insight into the germline and somatic drivers of cancer—including intragenic mutations, mutational signatures, amplifications, larger structural variants, and distinct patterns of gene expression. The publications went beyond "the usual suspects," and described the importance of non-coding changes, chromothripsis, and retrotransposons.

The Pan-Cancer Analysis of Whole Genomes Consortium reported that the average cancer has four or five driver gene mutations, that chromothripsis is a frequent and early event occurring in 20% of cancers, that deleterious germline variants are relatively common, and that these germline variants, in turn, affect the subsequent patterns of somatic mutations that occur in these cancers [2–7]. Addressing evolutionary processes that drive neoplasia, the consortium also bettered our understanding of the "clonal sweeps," which occur when a driver gene mutation gives a neoplastic cell a growth advantage [4]. Driver gene mutations tend to occur early in disease progression, while whole-genome duplications are late events [4].

The genetic changes driving ductal adenocarcinoma of the pancreas mirror those described in the Pan-Cancer Atlas by the Pan-Cancer Analysis of Whole Genomes Consortium [8]. Among them, two findings have potential to improve early detection and affect treatment options. First, a number of germline genetic variants that predispose to pancreatic cancer have been discovered. These can now be used to quantify risk, and several of these changes also create potential targets for therapeutic intervention [9]. Second, some of the somatic genetic changes are also therapeutically targetable, and, progress has even been made targeting the famously "undruggable" KRAS pathway [10–16].

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**Table 1** Inherited high-risk pancreatic cancer genes.

| Gene (Gene family) | Syndrome | Prevalence in pancreatic cancer patients (unselected) | Estimated relative risk vs. General population | Key points for pathologists/clinicians |
|---|---|---|---|---|
| *BRCA2* | Hereditary breast and ovarian cancer syndrome and Fanconi anemia | 2–7%[a] | 2.4–6.2 | Cancers may be very responsive to platinum-based therapy and to PARP inhibitors |
| *PALB2* | Hereditary breast and ovarian cancer syndrome and Fanconi anemia | <1%[a] | 2.4 | Cancers may be very responsive to platinum-based therapy and to PARP inhibitors |
| *BRCA1* | Hereditary breast and ovarian cancer syndrome and Fanconi anemia | 0.6–2.2% | 2.6 | Cancers may be very responsive to platinum-based therapy and to PARP inhibitors |
| *ATM* | Ataxia telangiectasia | 1.1–4.2% | 6 | Cancers may be responsive to radiation therapy |
| *STK11* | Peutz–Jeghers syndrome | <1% | 75–135 | Distinctive hamartomatous polyps |
| *P16/CDKN2A* | FAMMM | <1%–2.5 | 12–46 | Multiple dysplastic nevi should raise clinical suspicion |
| *PRSS1* and others | Hereditary pancreatitis | <1% | 50–60 | Increased risk of cancer limited to pancreas |
| *MLH1, MSH2, MSH6, PMS2* | Lynch syndrome | <1 | 6.6–8.6 | May have a medullary histology |
| *TP53* | Li Fraumeni syndrome | <1 | 6–7 | |

*FAMMM* familial atypical multiple mole melanoma.

[a]Prevalence higher among individuals of Ashkenazi Jewish Ancestry.

## Germline variants

One of the most consistent and remarkable findings across the sequencing of all cancer types is that a significant fraction (~ 10%) of all cancers arise in individuals with a germline variant that is associated with an increased risk of cancer [5]. Pancreatic cancer is no exception, and heritability studies have indicated that >20% of pancreatic cancer is due to inherited sequence variation [8, 17–19]. Looking back, this should not have been surprising. It has been known for decades that pancreatic cancer runs in some families, and that having multiple family members with pancreatic cancer increases an individual's risk of pancreatic cancer [20–25]. Prospective studies of families in which there had been a pancreatic cancer have allowed epidemiologists to develop risk prediction models, such as PancPRO, that can be used to estimate a person's risk of developing pancreatic cancer based on their family's cancer history [26, 27]. Prospective studies have also shown that relatives of patients with familial pancreatic cancer (defined as two first-degree relatives in a kindred with pancreatic cancer), also have an increased risk of death from breast, ovarian, and bile duct cancers [20]. Based on this strong epidemiologic background, "candidate gene approaches," the targeted sequencing of known cancer genes, were then undertaken and revealed that germline variants in *BRCA1*, *BRCA2*, *CDKN2A*, *PRSS1*, *STK11* and in the DNA mismatch repair genes can all increase the risk of pancreatic cancer [28–59]. Whole-exome and whole-genome sequencing followed and confirmed the importance of these genes, while also revealing that germline variants in *PALB2*, *ATM*, and other lower-prevalence genes increase the risk of developing pancreatic cancer (Table 1) [5, 8, 17, 60–62]. Importantly, as discussed below in the sections on specific genes, knowledge of each of these pancreatic cancer susceptibility genes now allows us to quantify cancer risk, and some of these variants create therapeutic targets [29–31, 41–43, 59, 63–69].

### Fanconi anemia pathway genes

Fanconi anemia, first described in 1927 by the Swiss pediatrician Guido Fanconi, is an autosomal recessive disease characterized by congenital abnormalities, defective hematopoiesis, and an increased risk of developing leukemia and solid malignancies [70]. The Fanconi anemia pathway functions to repair DNA damage, especially DNA interstrand crosslinks [70]. Deleterious germline variants in genes coding for members of the Fanconi anemia pathway, including *BRCA1*, *BRCA2*, and *PALB2*, increase the risk of developing cancer, including cancers of the breast, ovary, and, in some studies, prostate [33, 34, 66]. These germline variants also increase the risk of pancreatic cancer. Indeed, genes coding for members of the Fanconi anemia pathway

account for the largest fraction (10–20%) of the known pancreatic cancer susceptibility genes [35, 39, 71]. The demonstration of a second somatic hit, one inactivating the wild-type allele of the gene having the germline variant, further helped to establish a causative role for these genes in the development of pancreatic cancer [36, 59, 72, 73].

The identification of Fanconi anemia pathway genes as pancreatic cancer susceptibility genes allows one to now quantify risk. The risk of pancreatic cancer is elevated 2.4–6.2-fold in individuals who carry a deleterious germline *BRCA2* variant [31, 35, 66], and these *BRCA2* pathogenic variants occur in 2–7% of pancreatic cancer patients [31, 42, 43, 64, 65, 74–76]. The increased risk of pancreatic cancer is slightly lower (2.58-fold (95% CI, 1.54–4.05)) in individuals who carry a deleterious germline *BRCA1* variant, and these pathogenic variants in *BRCA1* occur in ~ 1% of patients with pancreatic cancer [31, 42, 43, 64, 75]. The risk of pancreatic cancer in carriers of pathogenic *PALB2* variants is not well established, with estimates ranging from 2.37 (95% CI, 1.24–4.50) in families identified through a breast cancer patient to 14.82 (95% CI 8.12–26.2) in pancreatic cancer patients undergoing genetic testing [42, 60, 75, 76]. This uncertainty is due to the relative rarity of pathogenic *PALB2* variants which occur in ~ 1% of all pancreatic cancer patients and up to 3% of familial pancreatic cancer patients [42, 60, 75, 76]. Finally, there have been isolated reports suggesting that other genes coding for members of this pathway, including *FANCA*, *FANCC, FANCG*, and *FANCM*, may contribute to the development of pancreatic cancer [43, 54, 77, 78].

Deleterious germline variants in *BRCA1* and *BRCA2* are more common in individuals of Ashkenazi Jewish heritage, helping to explain why pancreatic cancer is more common in this group [28, 36, 37, 59, 79]. Remarkably, deleterious germline variants in genes coding for members of the Fanconi anemia pathway have been reported in ~ 5% of pancreatic cancer patients without a family history of cancer [18, 29, 31, 44, 59, 67, 68, 75, 80, 81]. Because family history cannot be used to rule out a germline change, the National Comprehensive Cancer Network (NCCN) now recommends that all patients with pancreatic cancer undergo germline testing [82, 83].

Although the breast cancers arising in individuals with a deleterious *BRCA* germline variant are reported to often be triple-negative and to harbor high numbers of tumor-infiltrating lymphocytes, the histopathologic features of the pancreatic cancers that arise in individuals with a deleterious *BRCA* germline variant do not appear to be distinctive [84, 85]. Most are typical ductal adenocarcinomas.

As nicely described in the "Pan-Cancer Atlas," deleterious germline variants in *BRCA1*, *BRCA2*, and *PALB2* impact the subsequent somatic mutations that occur in the cancers [5, 86–88]. These deleterious germline variants are associated with increased numbers of small somatic deletions and somatic tandem duplications in the cancers [5]. In addition, these cancers harbor structural variants characteristic of "cycles of template insertions." These structural variants occur when small fragments of DNA copied from across the genome are joined together and then inserted into a derivative chromosome [5]. Pancreatic cancers from patients carrying one of these deleterious germline variants and having somatic inactivation of the wild-type allele, typically have an "unstable" genetic phenotype, with multiple chromosomal rearrangements, and are remarkably sensitive to treatment with DNA cross-linking agents, such as platinum-based drugs, and poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors [12, 32, 88–90]. For example, when compared with patients lacking a germline variant, complete pathologic responses are more likely in *BRCA2* carriers following neoadjuvant FOLFIRINOX therapy [91].

Unfortunately, resistant clones can emerge following these targeted therapies. Sequencing has identified some resistance mechanisms. It is likely that, among the billions of cancer cells in a tumor, there exist a few having a secondary mutation in the *BRCA2* gene, one that restores the gene back into a normal reading frame and re-establishes coding to synthesize a full-length protein [32, 92]. This returns normal (or near normal) function to the protein product, and under selective pressure, this small preexisting clone emerges as a dominant clone resistant to therapy [32, 92].

### *ATM*

The *ATM* gene encodes a phosphoinositide 3-kinase (PI3K) that functions in the PI3K kinase (PIKK) pathway [93, 94]. Through this pathway the protein product of the *ATM* gene coordinates the repair of double-stand DNA breaks [93, 94]. When a double-strand DNA break occurs, the ATM protein phosphorylates and thereby activates, a number of downstream proteins, which in turn result in DNA repair, cell cycle arrest, and in some cells apoptosis [93, 94]. Pathogenic germline *ATM* variants, including whole gene deletions, have been reported in ~ 3% of patients with familial pancreatic cancer [29, 62, 63, 68, 75, 76]. These pathogenic germline *ATM* variants are also present in ~ 2% of unselected patients with pancreatic cancer, indicating that, just as is true for patients with germline pathogenic *BRCA* gene variants, not all patients with a deleterious germline *ATM* variant have a family history of cancer [18, 29, 43, 62, 68, 76, 80, 94]. Germline pathogenic variants in *ATM* are estimated to increase the risk of pancreatic cancer ~ 5.71-fold (95% CI, 4.38–7.33) [31].

At the light microscope level, there is a hint that patients with a deleterious germline *ATM* variant are slightly more

likely to develop cancers with a colloid morphology, but the majority of pancreatic cancers that arise in patients with a germline *ATM* mutation are standard infiltrating ductal adenocarcinomas [95]. Pathogenic germline *ATM* mutations have also been described in 1.6% of patients with intraductal papillary mucinous neoplasms (IPMNs) who underwent surgical resection, suggesting that the IPMN precursor pathway may be taken by some of these pancreatic cancers [96]. Although this fits with the observation of an increased prevalence of colloid carcinomas in patients with deleterious germline *ATM* variants, as almost all colloid carcinomas of the pancreas arise in association with intestinal-type IPMNs, the complete progression from germline ATM variant, to intestinal-type IPMN to invasive colloid carcinoma has not been established [97].

Just as was true for germline pathogenic *BRCA* variants, germline pathogenic *ATM* variants may confer specific therapeutic sensitivities. *ATM* inactivation is predicted to inhibit the repair of double-stand DNA breaks, thereby increasing genomic instability and increasing sensitivity to radiation therapy and to platinum-containing drugs, as these therapies induce double-strand breaks [93, 94, 98]. Although *ATM* mutated cells were reported to be sensitive to PARP inhibitors in vitro, studies to date have not demonstrated these drugs to be effective in genetic models or in patients with *ATM* mutations [99, 100]. In addition, a number of compounds are now available to target the ATR-checkpoint kinase 1 (Chk1) pathway, including compounds that target ATR and Chk1 (a serine/threonine kinase functioning downstream of ATR), and pancreatic cancers with loss of ATM-mediated DNA repair may show increased sensitivity to one of these [93, 94].

### *CDKN2A*

Germline mutations in the *CDKN2A* gene cause the familial atypical multiple mole melanoma (FAMMM) syndrome [101]. FAMMM, as the name suggests, is characterized by multiple melanocytic nevi, some of which are dysplastic, and an increased risk of melanoma (Fig. 1). In addition, individuals who inherit a germline *CDKN2A* gene mutation have a 17% risk of developing pancreatic cancer by the age of 75 [43, 45, 46, 102–105]. Indeed, deleterious germline variants in the *CDKN2A* gene are found in about ~1% of pancreatic cancer patients; the risk of pancreatic cancer has been estimated to be 12–46-fold greater in carriers of one of these variants than in the general population [18, 29, 31, 42, 54, 68, 80, 103, 106]. The risk of pancreatic cancer may be even higher in carriers of deleterious *CDKN2A* variants who smoke cigarettes [49]. Multifocal pancreatic cancers have been reported in some patients with pathogenic germline *CDKN2A* variants [102]. Not everyone with a deleterious germline variant has a personal or family history of melanoma, adding support to the NCCN guidelines recommending universal germline testing in all patients with pancreatic cancer [45, 50, 75].

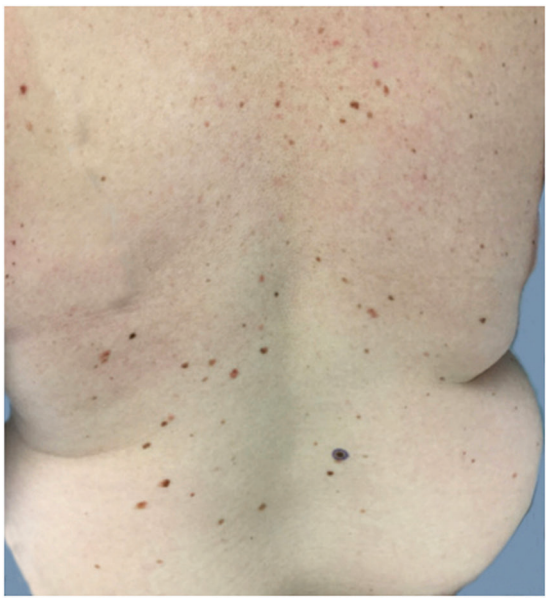

**Fig. 1 A patient with familial atypical multiple mole melanoma syndrome (FAMMM).** Note the numerous melanocytic nevi. (Courtesy of Elise Ng, MD).

The pathology of the pancreatic cancers that develop in these patients does not appear to be specific, however, there have been reports of cancers with prominent squamous features [107]. Since melanomas can be detected with a simple skin exam, the identification of a germline *CDKN2A* variant does allow one to go back to carriers in an affected family and detect early, curable melanomas [50].

### Lynch syndrome

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, is characterized by an increased risk of developing numerous cancers especially colorectal, endometrial, brain, ovary, gastric, small intestine, urothelial, and pancreatic cancer [56, 108, 109]. Germline variants in genes coding for proteins that function in DNA mismatch repair, e.g., *MLH1*, *MSH2*, *MSH6*, and *PMS2* cause Lynch syndrome [18, 29, 32, 54, 55, 58, 64, 68, 75, 76, 80, 110]. Pathogenic germline variants in the genes associated with Lynch syndrome occur in <1% of pancreatic cancer patients, and individuals with Lynch syndrome have a 6–8.6-fold increased risk of developing pancreatic cancer [31, 56, 58, 111]. As is true for the other germline changes associated with an increased risk of pancreatic cancer, germline variants in DNA mismatch repair genes have been reported in unselected individuals with pancreatic cancer [29, 68, 80]. The pancreatic cancers that arise in patients

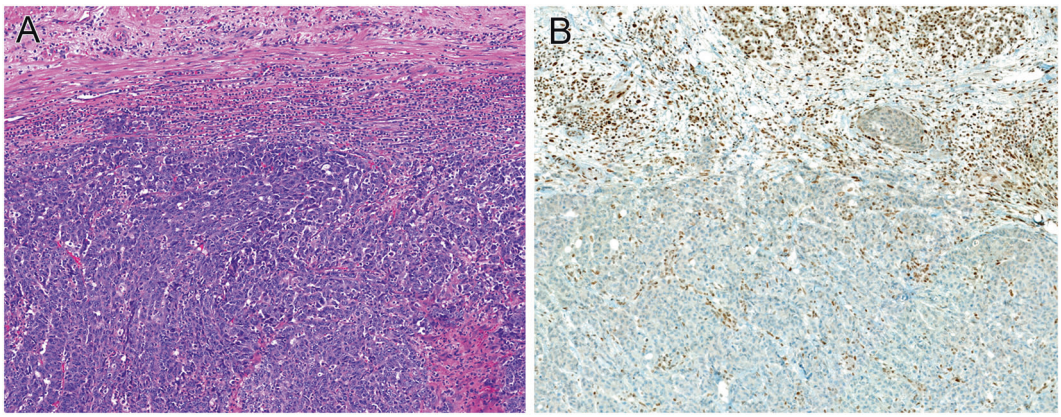


**Fig. 2 Medullary carcinoma of the pancreas.** These cancers are often microsatellite unstable. Note the pushing boarder and syncytial growth pattern (**a**), and the loss of expression of the mismatch repair protein MLH1 (**b**). (**a** hematoxylin and eosin stain; **b** immunolabeling for MLH1).

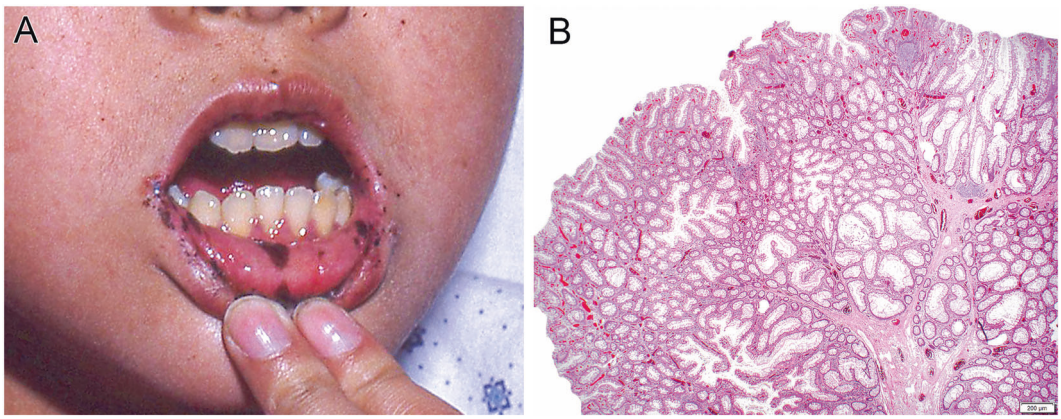


**Fig. 3 Peutz–Jeghers syndrome.** Note the melanocytic macules on the lips and buccal mucosa in **a**, and the classic hamartomatous polyp in **b**. (**a** courtesy of Sewon Kang, MD. **b** is a hematoxylin and eosin stain).

with the Lynch syndrome often have a distinct "medullary" histology (Fig. 2), although acinar cell and other carcinomas can also occur, and not all pancreatic cancers with a medullary appearance have an alteration in a DNA mismatch repair gene [112–115]. Of note, the vastly increased numbers of somatic mutations that accumulate in these cancers result in the expression of altered proteins that can serve as "neoantigens" to the immune system [86]. Therefore, these cancers are often accompanied by a brisk immune response, which includes activated CD8-positive T cells [86]. All of this, of course, has profound therapeutic implications, as microsatellite-unstable (MSI-high) cancers often respond well to treatment with immune checkpoint inhibitors [11, 12, 15, 116, 117].

## Peutz–Jeghers

The Peutz–Jeghers syndrome, described as early as 1895, was first characterized by Jan Peutz in 1921 [118]. The full syndrome was then described in 1949 by Harold Jeghers [118]. Peutz–Jeghers is characterized by melanocytic macules involving the lips and buccal mucosa (Fig. 3a), distinctive hamartomatous polyps of the gastrointestinal tract (Fig. 3b), and a dramatically increased risk of cancer [119]. Peutz–Jeghers syndrome is caused by germline pathogenic variants in the *STK11* gene (also known as *LKB1*) on chromosome 19p. *LKB1* codes for a serine threonine/kinase that plays a role in energy metabolism and cell polarity. Individuals having the Peutz–Jeghers syndrome have an increased risk of developing cancer of the lung, breast, ovary, and pancreas [52, 53, 120]. The risk of pancreatic cancer is 75–135 times greater than that of the general population [52, 53, 120]. Korsse et al. estimated that patients with Peutz–Jeghers have a 26% chance of developing pancreatic cancer by the age of 70 [53]. Although the risk in each individual is greatly increased, the syndrome itself is relatively rare, and it accounts for <1% of all pancreatic cancers [52, 53, 120]. The pathology of the Peutz–Jeghers syndrome is well-described. In addition to the characteristic hamartomatous polyps of the

gastrointestinal tract, some patients develop IPMNs of the pancreas [121]. The invasive cancers of the pancreas are usually conventional ductal adenocarcinomas.

## Hereditary pancreatitis

Hereditary pancreatitis is characterized by the early onset of recurrent bouts of severe pancreatitis. It is caused by germline pathogenic variants in *PRSS1, SPINK1*, and other genes [51]. Individuals with hereditary pancreatitis have an extraordinarily high risk of developing pancreatic cancer. Their risk is elevated 50–60-fold, and some series report that the risk approaches 40% by the age of 70 [122–127]. The risk of developing pancreatic cancer is especially high in individuals with hereditary pancreatitis who also smoke, and the cancers that arise in these smokers develop years earlier than those that arise in non-smokers [123, 124]. The pancreas pathology associated with hereditary pancreatitis has been described and, in addition to the changes of chronic pancreatitis, includes pancreatic intraepithelial neoplasia (PanIN) lesions [128, 129]. In the report by Rebours et al., these included high-grade PanIN lesions, while Singhi et al. reported only low-grade PanIN (PanIN-1A) [128, 129]. Unlike the other familial pancreatic cancer syndromes, the risk of cancer in individuals with hereditary pancreatitis is confined to the pancreas. Since increased risk of cancer is confined to pancreas, and the repeated bouts of pancreatitis badly damage the pancreas, some patients have elected to undergo prophylactic pancreatectomy. An excess of pathogenic variants in the pancreatitis susceptibility gene *CPA1* and the related gene, *CPB1*, have been observed in patients with pancreatic cancer compared with controls, suggesting that these variants can predispose to pancreatic cancer without the clinical syndrome of pancreatitis [17, 130].

## Other pancreatic cancer susceptibility genes

Germline variants in a number of other genes are associated with an increased risk of pancreatic cancer, but, judging from these reports, pathogenic variants in these genes are less prevalent as compared with those described above. These genes include *APC*, *BARD1*, *BUB1, BUB3, BAP1, CHEK2, FAM175A, FAN1, NEK1, POLQ, RABL3, RAD50, RHNO1, SKIL, SMG1, TP53, TUBB5*, and others [18, 29–31, 43, 59, 61, 68, 75, 80, 131–134]. Several of these genes are of note. Hu et al. estimated that germline *TP53* mutations increase the risk of pancreatic cancer 6.7-fold [31]. Although *APC* is included on this list, one has to be careful interpreting the cancers that arise in individuals with germline *APC* mutations as these patients have an increased risk of duodenal and ampullary cancers, and both of these cancers can invade into the pancreas and mimic pancreatic cancer [135]. *SKIL* and *TUBB5* are on this list because of the remarkable report of an infant with germline *SKIL* and *TUBB5* variants who developed a large IPMN [61, 136]. Of note, *TUBB5* is in the robo-slit pathway, and somatic mutations in genes coding for members of this pathway have been described in sporadic pancreatic cancers [136]. Certainly, based on the findings of whole-genome sequencing, there are other, yet to be discovered, pancreatic cancer susceptibility genes [17].

## Moderate/low-risk pancreatic cancer loci

While we have focused on the rare deleterious germline variants having high penetrance, it should be noted that there are also many more common, lower-penetrance genetic variants that impact the risk of pancreatic cancer ever so slightly. These have been identified by genome-wide association studies (GWAS) in which the prevalence of these genetic variants in large populations of individuals with the phenotype (pancreatic cancer) were compared with the prevalence of these variants in individuals free of pancreatic cancer. A number of such GWAS have been performed, revealing genetic loci associated with a slightly increased pancreatic cancer risk [137]. In European populations, these loci include 1q32.1 (*NR5A2*), 1p36.33 (NOC2L), 2p13.3 (*ETAA1*), 3q29 (*TP63*), 5p15.33 (*CLPTM1L, TERT*), 7p14.1 (*INHBA*), 8q21.11 (*HNF4G*) 8q24.21 (*MYC*), 9q34.2 (ABO), 13q12.2 (*PDX1*), 13q22.1 (*KLF5*), 16q23.1 (*BCAR1*), 17q12 (*HNF1B*) 17q25.1 (*LINC00673*), 18q21.32 (*GRP*), and 22q12.1 (*ZNRF*) [137–140]. Additional GWAS studies have been conducted in both in Chinese and Japanese populations, with five loci 21q21.3, 5p13.1, 21q22.3, 22q13.32, and 10q26.11 reported to be associated with pancreatic cancer in the Chinese population, and 6p25.3, 12p11.21, and 7q36.2 in the Japanese [141, 142]. The ABO locus is particularly interesting as non-O blood type increases risk [137, 143]. The mechanisms driving this association are unclear.

## Screening in familial syndromes

In addition to guiding precision therapy for patients known to have pancreatic cancer, an understanding of the genetic drivers of the familial aggregation of pancreatic cancer has implications for early detection. As genes are identified, the risk each variant carriers can be quantified, and used to prioritize people for screening with the goal of detecting early, curable pancreatic and extra-pancreatic neoplasms [104]. Individuals with both a family history and a pathogenic germline variant may benefit most, as they have been found to be at the highest risk of pancreatic cancer in screening studies, compared with individuals with a family history by no identifiable mutation [144]. Several screening approaches have been taken, but most rely on endoscopic

ultrasound (EUS) combined with magnetic resonance imaging or computed tomography (CT) scanning [145–147]. Preliminary results from EUS-based screening trials have demonstrated that asymptomatic precursor lesions and, rarely, early curable cancers can be detected, and SEER data hint that more early stage cancers are now being detected nationally [145–149]. Consensus guidelines currently recommend pancreatic surveillance for individuals at the highest estimated risk, it has, however, yet to be demonstrated that screening for pancreatic cancer saves lives [150]. Because of the role of environment and chance in the development of cancer, accurately predicting an individual's risk of developing cancer remains elusive [150, 151]. As discussed later, there is also a risk that screening will detect harmless lesions and, in so doing, will lead to patient harm through unnecessary interventions [152, 153].

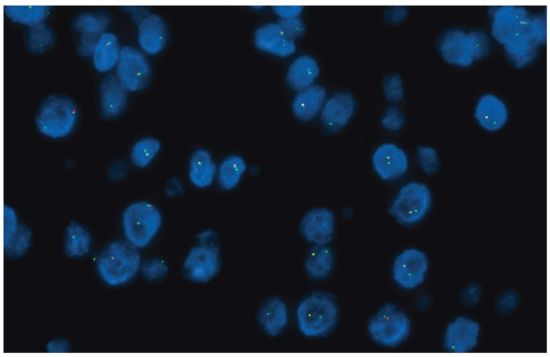

**Fig. 4 Intraductal oncocytic papillary neoplasm (IOPN) with a characteristic *PRKACA* fusion.** The fusion has resulted in loss of the 5′ probe (red) for *PRKACA* in this fluorescent in situ hybridization. (3′*PRKACA*[19p13.12](Green)/5′*PRKACA*[19p13.12](Red)) (Courtesy of Michael Torbenson).

## Precancers

A number of morphologically distinct precancerous lesions have been identified and characterized in the pancreas. These range from microscopic PanIN lesions, to larger macroscopic lesions such as IPMNs and mucinous cystic neoplasms (MCNs) [135, 154, 155]. Rather than review each lesion, here we will focus on key recent advances. We will then expand on the clinical implications of these advances, with an emphasis on clinical cyst fluid testing.

### The four most common cystic neoplasms of the pancreas

There are four main cystic neoplasms of the pancreas [135, 155]. In addition to IPMNs and MCNs, these include solid pseudopapillary neoplasms (SPNs) and serous cystic neoplasms (SCNs). Of these four, IPMNS and MCNs are precancerous lesions; some IPMNs and some MCNs progress over time to invasive carcinoma. By contrast, all SPNs are low-grade malignancies, and essentially all SCNs are benign [135, 155]. Distinguishing among these cystic neoplasms is therefore important.

IPMNs are of particular note, for they are detectable using currently available imaging and are now the most commonly surgically resected cystic neoplasm of the pancreas [156]. IPMNs therefore probably represent the best opportunity to detect and treat precancers before they progress to an incurable invasive cancer. The challenge is that IPMNs are remarkably common, and most do not progress to invasive cancer, and there therefore is a real risk of causing harm by over treating those lesions that would remain harmless [157].

With the goal of improving the preoperative classification of these neoplasms, the exomes of a series of well-characterized cystic neoplasms of the pancreas were sequenced a decade ago [158, 159]. IPMNs were found to have somatic mutations in *GNAS* and *RNF43*, as well as mutations in three of the genes frequently targeted in invasive ductal adenocarcinomas of the pancreas (*KRAS*, *TP53*, and *CDKN2A*) [158–161]. By contrast, it was recently shown that the morphologically distinct intraductal neoplasm, the intraductal oncocytic papillary neoplasm (IOPN), does not harbor these changes and, instead, IOPNs have distinctive translocations targeting the *PRKACA* or *PRKACB* genes (Fig. 4) [162, 163]. Importantly, as shown in Table 2 and illustrated in Fig. 5, these patterns of mutations differ significantly from those seen other cystic neoplasms in the pancreas [158–161]. SPNs have mutations in the gene coding for beta-catenin (*CTNNB1*), SCNs have somatic mutations in *VHL*, and the mutational spectrum seen in MCNs closely matches that of IPMNs, except *GNAS* mutations are rare in MCNs [158–161, 164]. Of note, mutations and allelic losses in IPMNS and in MCNs appear to accumulate with the degree of dysplasia, such that higher degrees of aneuploidy are seen in lesions with high-grade dysplasia than in lesions with low-grade dysplasia [158, 165, 166].

Importantly, neoplastic cells shed mutant DNA into cyst fluid, suggesting that sequencing of cyst fluid could be used clinically to determine cyst type and potentially even the grade of dysplasia [160–162, 167, 168]. This indeed appears to be the case. Cysts can be aspirated at the time of EUS, and genetic analysis of cyst fluid can help define the cyst type [160, 161, 167, 168]. The sensitivity and specificity of these analyses can be improved when genetic findings are combined together with protein biomarkers and with clinical findings [167, 168]. For example, the cyst fluid of SPNs harbor a *CTNNB1* gene mutation, and SPNs almost always occur in young women [164, 167, 168]. By contrast, high levels of vascular endothelial growth factor-A are present in the cyst fluid of SCNs, SCNs often harbor *VHL* gene mutations, and SCNs have a characteristic sponge-like

**Table 2** Genetic alterations in cystic neoplasms.

| Cyst type | Genes | Clinical findings/proteins in cyst fluid | Malignant potential | Implications for pathologists |
|---|---|---|---|---|
| Intraductal oncocytic papillary neoplasm | *ATP1B1-PRKACB, DNAJB1-PRKACA*, or *ATP1B1-PRKACA* fusions | Intraductal growth | Can progress to invasive cancer | Rare, genetic alterations parallel those of fibrolamellar carcinoma of the liver |
| Intraductal papillary mucinous neoplasm | *KRAS, GNAS, RNF43, CDKN2A*, and *TP53* (especially high-grade) | Intraductal growth, Fukuoka criteria guide management, high amylase as these connect with duct, high CEA in higher-grade | Can progress to invasive cancer | Very common neoplasm. Grade is important in assessing risk of progression, but grade can be hard to determine preoperatively |
| Intraductal tubulopapillary neoplasm | Loss of *CDKN2A* in 25%, *FGFR2* fusions | Intraductal growth | Can progress to invasive cancer | Rare, histologic appearance mimics that of cribriform intraductal carcinoma of the breast. Some genetic alterations are potentially therapeutically targetable |
| Mucinous cystic neoplasm | *KRAS, RNF43, CDKN2A*, and *TP53* (especially high-grade) | Tail of the gland, women, low amylase, high CEA in higher-grade | Can progress to invasive cancer | Ovarian stroma is diagnostic |
| Serous cystic neoplasm | *VHL* | Central stellate scar, VEGFA in cyst fluid | Almost all benign | Avoid resection if small and asymptomatic |
| Solid pseudopapillary neoplasm | *CTNNB1* (beta-catenin) | Women | All are low-grade malignant | Touch preparations extremely helpful, as is immunolabeling for beta-catenin. Potentially targetable genetic alteration |

*CEA* carcinoembryonic antigen, *VEGF* vascular endothelial growth factor.

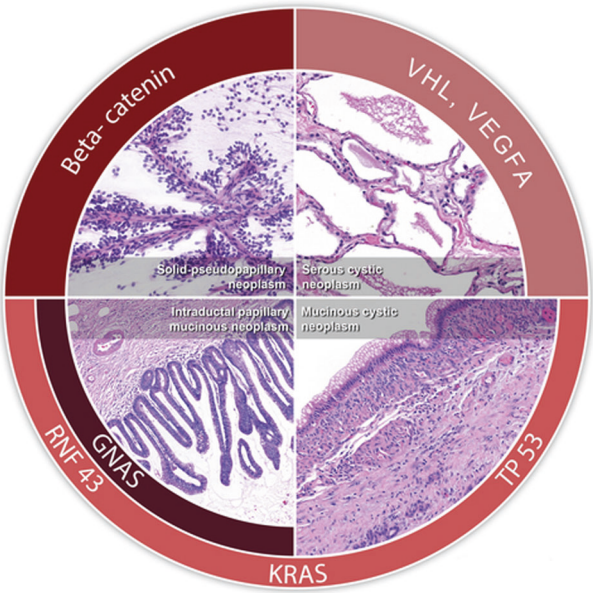


**Fig. 5 The characteristic changes in the four most common cystic neoplasms of the pancreas.** *VEGFA* vascular endothelial growth factor-A.

appearance on CT scanning [167–169]. These findings provide great hope for improved preoperative diagnoses. As discussed in the next section, however, the pathology of cystic neoplasms presents real challenges to clinical cyst testing.

## Challenges in the genetic analysis of cyst fluid

The first challenge is that clinical management of cystic neoplasms is not simply driven by cyst type. For example, IPMNs are common, and while some will progress to invasive cancer, most do not [149, 170, 171]. The goal is to resect those IPMNs that are likely to progress, and to observe those that are unlikely to progress [172]. Because the grade of dysplasia is an indicator of the risk of progression, preoperative tools to determine the degree of dysplasia are needed. This turns out to be much harder than determining the cyst type. Although some somatic mutations, such as inactivating mutations in the *TP53* gene, are more common in IPMNs with high-grade dysplasia, no single specific genetic change correlates perfectly with dysplasia [160, 161, 167, 168]. Instead, the accumulation of multiple genetic changes, including the development of significant aneuploidy, appears to be most useful [165, 173, 174]. Ultimately, it is likely that a combination of clinical features (imaging, symptoms) and cyst fluid biomarkers (intragenic mutations, aneuploidy, and protein) will be required to assess risk [172].

A second significant hurdle in clinical cyst fluid analysis is that most cystic neoplasms do not form a single locule [135, 155]. Instead, they form multiple locules, and the degree of dysplasia in one locule often does not match the degree of dysplasia in the other locules (Fig. 6) [175–177]. The implications of this are profound. It means that, even

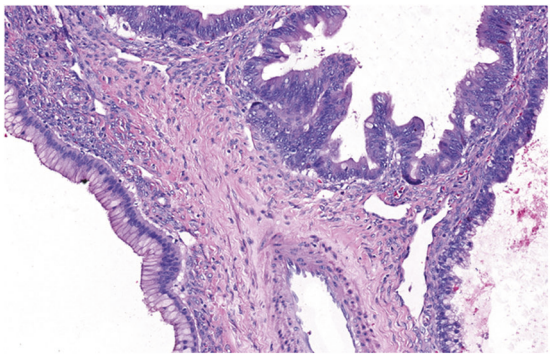

**Fig. 6 Mucinous cystic neoplasm of the pancreas.** Note the dramatically different degrees of dysplasia in the three locules. (Hematoxylin and eosin stain).

with a perfect test, the findings in the fluid aspirated from one locule of a multi-locular cystic neoplasm may not reflect the pathology in the other locules.

Third, in addition to heterogeneity among the different locules, there appears to also be significant genetic heterogeneity within individual locules [174, 175, 177]. This has been demonstrated with sequencing and has been visualized with mutation-specific in situ hybridization probes. For example, single-cell sequencing of ten IPMNs revealed that different mutations in the same driver gene frequently occur in the same IPMN [177]. Different neoplastic clones within a single IPMN will grow at different rates, and new clones can emerge and out compete existing clones [174, 177]. While this heterogeneity can complicate cyst fluid analysis, it can also provide insight into the progression of a neoplasm as there is often a loss of heterogeneity as a single-dominant high-grade clone emerges and outgrows the clones with lower grade dysplasia [174, 175, 177].

Further complicating cyst fluid analysis, there can be heterogeneity within the broader pancreas. Perhaps the best example of this is the observation that invasive cancers that arise adjacent to a well-defined IPMN may be genetically unrelated to that IPMN [174, 176]. Clinically important neoplasms can arise from areas of the pancreas unrelated to the cyst itself, and the likelihood that two lesions are genetically distinct grows with greater anatomic separation. Thus, even if we characterize an IPMN perfectly, we are not characterizing the entire pancreas in its totality.

We have saved the pièce de résistance for the last part of this discussion, as it is now clear that neoplastic cells can move within the duct system [178, 179]. This had been observed earlier with invasive carcinoma. In a process called cancerization of the ducts, invasive carcinoma within the stroma can grow into and along the internal surface of a preexisting pancreatic duct [178]. Similarly, the spread of neoplastic cells of non-invasive IPMNs within the duct system has been demonstrated through the genetic analyses of IPMNs that recurred after surgery [179, 180]. Surgically resected non-invasive IPMNs with negative surgical margins can recur in the remnant pancreas, and in some, but not all, instances the recurrent IPMN in the remnant pancreas harbors identical mutations as those present in the originally resected IPMN [179, 180]. The movement of neoplastic cells within the duct system means that the neoplastic cells, even of a well-delineated IPMN, are not always limited to the grossly visible lesion. The remainder of the grossly uninvolved pancreas remains at risk owing to "seeding" from the original IPMN. Indeed, the movement of neoplastic cells within the duct system of the pancreas partially explains why the entire pancreas appears to be at risk when a patient has an IPMN [181–183]. This is especially true for main-duct IPMNs [182]. In one study of over a thousand patients who were followed after the surgical resection of an IPMN, 14.4% developed a recurrence [183]. Clinically, this suggests that patients with an IPMN need to be followed carefully, even if that IPMN is resected.

Thus, although great progress has been made, there are still significant unanswered questions that fundamentally impact the management of precancerous lesions. Perhaps the big unanswered question is—why is the entire pancreas at risk in patients with an IPMN [102, 179]?

## Invasive cancers

### Recent advances

The genes targeted with somatic mutations in pancreatic cancer have been well-characterized (Table 3). These include the now famous "four mountains" (present in >50% of the cancers), *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, as well as a long list of genes targeted less frequently [1, 8, 88]. Alterations in some of these genes, as illustrated in Fig. 7, can be used to aid diagnoses.

The whole-exome and whole-genome sequencing efforts of the last decade have created a more complete list of targeted genes, and a more complex picture of pancreatic cancer is now emerging [1, 8, 88]. This picture includes intragenic mutations, homozygous deletions, amplifications, dramatic shattering of chromosomes (chromothripsis), the activation of transposons, and intragenic mutations coupled with copy number changes of the same gene [3, 184].

Chromothripsis is the dramatic sudden shattering of a chromosome, or of part of a chromosome, followed by massive genomic rearrangements as the bits of the shattered pieces reassemble [3, 184]. Chromothripsis can result in the amplification of oncogenes, and the inactivation of tumor suppressor genes. Chromothripsis is pervasive across many cancer types, and occurs in almost two-thirds of pancreatic cancers [3, 184]. The suddenness of chromothripsis makes it tempting to speculate that chromothriptic events cause the

**Table 3** Genes somatically targeted in pancreatic cancer.

| Gene | Chromosome | Gene type | Type of alteration | Percentage of cancers with alteration | Implications for pathologists/clinicians |
|---|---|---|---|---|---|
| *KRAS* | 12p | Onc | IM, rarely amplified | 95 | |
| *CDKN2A* | 9p | TSG | HD, LOH + IM, Meth | 95 | |
| *TP53* | 17p | TSG | LOH + IM | 75 | |
| *SMAD4* | 18q | TSG | HD, LOH + IM | 55 | IHC can be used to determine if a lesion is likely to be a metastasis from a pancreatic primary |
| *ARID1A* | 1p | TSG | IM + LOH | 3 | |
| *RNF43* | 17q | TSG | IM + LOH | <10 | IPMN associated PDAC |
| *GNAS* | | Onc | IM | <5 | IPMN associated PDAC |
| *TGFβR2* | 3p | TSG | IM + LOH, HD | <5 | |
| *TGFβR1* | 9q | TSG | HD | <1 | |
| *FBXW7* | 4q | TSG | LOH + IM | 3 | |
| *MYC* | 8p | Onc | Amp | 5–10 | Potentially therapeutically targetable |
| *GATA6* | 18q | Onc | AMP | <5 | Tend to have a "classical" pattern of RNA expression. |
| *ERBB2* | 17p | Onc | Amp + IM | 1 | Therapeutically targetable |
| *BRAF* | 7q | Onc | IM, deletion | <5 | Potentially therapeutically targetable |
| *AKT2* | 19q | Onc | Amp | <5 | |
| *ATM* | 11q | TSG | IM + LOH | 1–5 | Potentially therapeutically targetable |
| *BRCA2* | 13q | TSG | IM + LOH | 1–5 | Therapeutically targetable |
| *MLH1* | 3p | MMR | IM LOH, Meth | 1 | Immune checkpoint inhibitors |
| *NRG1* | | | Fusions | <5 | Therapeutic target of KRAS wild-type PDAC |
| *KDM6A* | X | TSG | IM + LOH | 3 | |
| *STK11* | 19p | TSG | IM + LOH | 1 | |
| *RB1* | 13q | TSG | IM + LOH | 1–2 | |
| *ACVR1β* | 12q | TSG | HD, LOH + IM | <1 | |
| *ACVR2* | 2q | TSG | HD, LOH + IM | <1 | |
| *ROBO2* | 3p | TSG | LOH | 1–2 | |
| *PIK3CA* | 3q | Onc | | 1–3 | Potentially therapeutically targetable |
| *CCNE1* | 19p | Onc | Amp | <1 | |
| *NTRK1* | 1q | Onc | Fusion | <1 | Potentially therapeutically targetable |
| *CDK4* | 12q | Onc | Amp | <1 | Potentially therapeutically targetable |
| *CDK6* | 7q | Onc | Amp | <1 | Potentially therapeutically targetable |
| *FGFR1* | 8p | Onc | Amp | <1 | Potentially therapeutically targetable |

*AMP* amplification, *HD* homozygous deletion, *IG* intragenic, *IHC* immunohistochemical labeling, *LOH* loss of heterozygosity, *Meth* aberrant methylation, *MMR* DNA mismatch repair, *Onc* oncogene, *Repair* DNA repair gene, *TSG* tumor suppressor gene.

apparent sudden aggressiveness that can be seen clinically in some patients with pancreatic cancer [184]. However, the magnitude of the overall contribution of chromothripsis to the pathogenesis of pancreatic cancer is yet to be determined, as many chromothriptic events in pancreatic cancer do not target well-defined oncogenes or tumor suppressor genes [3, 184, 185]. New technologies could help define the impact of chromothripsis. Currently, the detection of chromothripsis requires deep sequencing. The development of novel methods to detect chromothripsis in situ would allow investigators to determine when chromothripsis occurs in neoplastic progression, and then perhaps, correlate the timing with the patient's clinical status. For example, if chromothripsis occurs as a primary cancer explosively metastasizes, this temporal association would suggest that the event is clinically important.

The last decade was also marked by advances in our understanding of the role played by mobile DNA elements in the development of pancreatic cancer [7, 186, 187]. The open reading frame 1 protein, ORF1p, is encoded by a long interspersed element-1 (LINE-1) retrotransposon, and novel LINE-1 insertions and ORF1p overexpression have been

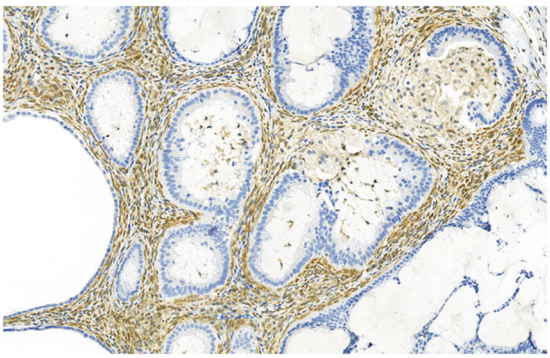

**Fig. 7 Loss of SMAD4 protein in a pancreatic cancer metastatic to the ovaries.** The patient's primary pancreatic cancer showed loss of SMAD4 as did the adenocarcinoma involving both ovaries. This pattern supports the diagnosis that the adenocarcinoma in the ovaries was a metastasis from the patient's pancreatic primary. (Immunolabeling for SMAD4).

documented in pancreatic cancer [186, 187]. These somatically acquired LINE-1 insertions could, plausibly, influence gene expression, and Ardeljan et al. recently suggested that these insertions may create a unique vulnerability that could be exploited therapeutically [188]. The complexity of mobile DNA elements makes them hard to study; emerging technologies, however, offer promise to clarify the mechanisms and roles that these elements have in disease [189, 190].

For decades, activating point mutations in the *KRAS* oncogene were known to be important drivers of pancreatic cancer [191]. More recently, it has been shown that copy number changes in the *KRAS* gene are also important [14, 191, 192]. The intragenic mutations that activate the KRAS protein have a number of downstream effects, including increasing glucose uptake, a shift to aerobic glycolysis, and ultimately the promotion of proliferation, invasion, and cell survival [14]. Recently, single-cell analyses supported suggestions that somatic copy number changes in the *KRAS* gene also promote tumorigenesis [192]. For example, Chan-Seng-Yue et al. described amplifications of mutant *KRAS*, relative to the wild-type allele, which create allelic imbalances favoring the mutant allele [192]. Genomic duplication appears to drive these imbalances in mutant *KRAS* copy number, and it has been reported that primary pancreatic cancers with *KRAS* copy number events are more likely to be of the more aggressive basal subtype, often with squamous differentiation (see below) [192]. Studies of recurrent PDAC find evidence of convergent evolution on the KRAS pathway with mechanisms including multiple routes to copy number gain of mutant *KRAS*, multiple different *KRAS* mutations in different metastatic clones and mutations in other components of the KRAS/MAPK/ERK pathway [193].

Copy number changes, such as those seen with *KRAS*, are a component of the larger and nearly ubiquitous (except for the cancers with MSI) phenomenon of aneuploidy in pancreatic cancer. The *FAM190A* gene occupies a hotspot of genomic homozygous deletions, producing deletions of internal exons, and, in turn, creating in-frame deletions of the protein-coding sequence [194, 195]. In addition, more than a third of pancreatic cancers have similar in-frame deletions within *FAM190A* transcripts, which are manifest without an identifiable genomic mutation. Functional studies of genetically engineered cells and protein localization techniques show that Fam190a normally functions in mitosis to ensure the creation of mononuclear daughter cells after the abscission (separation) phase of mitotic division, thus avoiding a simple cause of polyploidy [196]. The common Fam190a abnormalities thus might spur chromosomal instability during tumorigenesis and, specifically, could help explain the common finding of tetraploidy in pancreatic cancers [192].

A great deal of effort in the last decade has gone into defining "molecular" (gene expression) subtypes of pancreatic cancer with mixed results [197–200]. It is now clear that contaminating non-neoplastic cells often confound these studies, and subtypes with "exocrine differentiation" almost certainly simply reflect the contamination of cancers with non-neoplastic acinar cells [8]. When non-neoplastic contamination is taken into account, two broad subtypes do consistently emerge [8, 199]. Cancers of the "classical" subtype often have *GATA6* gene amplification, and a classic ductal differentiation. The "basal-like" subtype, as noted above, are more likely to have *KRAS* gene copy number changes, and a worse prognosis [8, 192, 199, 201]. While the subtyping of pancreatic cancer based on patterns of RNA expression has proven prognostically valuable, it should be noted that expression patterns in a cancer are not fixed [192]. They can change over time, and can differ in different areas of a tumor [192]. We believe that the subtyping of pancreatic cancer will be most impactful when RNA and protein expression patterns are correlated with tumor morphology.

The clinical application of molecular pathology to pancreatic cancer is becoming increasingly challenging. Low tumor cellularity (<10%) puts detection of mutations just around the limit of detection of most next generation sequencing assays (commonly ~5%). This is becoming even more difficult in the era of neoadjuvant therapy, which if successful, can result in extremely low neoplastic cellularity in the resected tumor.

## Early detection

Most patients with pancreatic cancer are not diagnosed until their disease is advanced [202]. Not surprisingly, it has been predicted that pancreatic cancer will soon become the second

leading cause of cancer death in the United States and in other countries [203, 204]. As a result, there is a great deal of interest in harnessing the power of genetics for the earlier detection of pancreatic cancer [205–207]. Given the specificity of somatic mutations for the presence of a clone of cells, the detection of circulating tumor DNA (ctDNA) provides a promising foundation for the early detection of pancreatic cancer [207]. Extremely sensitive and specific tests for ctDNA have been developed, and when applied clinically these have been very specific, but only moderately sensitive in detecting ctDNA in patients known to have a cancer [205–208]. Other approaches, including those based on detecting fragmented DNA of specific lengths and the detection of aneuploidy, have been developed that should improve the accuracy and usefulness of blood tests [205, 209, 210]. In addition, a number of genes are abnormally methylated in pancreatic cancer, and several approaches have been developed to detect aberrant methylation patterns in blood, pancreatic juice, and pancreatic cyst fluid [211–216].

As exciting as these advances are, significant hurdles remain to developing an effective screening test for pancreatic cancer. One major challenge confronting the screening for pancreatic cancer is its rarity in the general population at any point in time [152, 153]. As a result, even a highly specific screening test will generate many false positive results relative to the true positives [152, 153]. Indeed, the costs, including financial, psychological, and patient harm from unnecessary procedures, currently outweigh the benefits [152, 153].

Even if a perfect test were developed, it might never be possible to detect curable pancreatic cancers, as the window of opportunity for the detection of curable pancreatic cancer is likely extremely short in some patients. For example, several studies have shown that even early pancreatic cancers invade veins within the pancreas [202, 217, 218]. These veins drain directly into the liver, suggesting that early liver metastases may be almost universal in pancreatic cancer [202, 217, 218]. As a result, today, the clinical use of ctDNA testing is limited to following the response of patients with a known cancer to therapy [219]. Given the increase in therapeutic options and given the speed at which a given patient develops resistance to therapy, it seems likely that the use of ctDNA to guide therapy will increase in the coming decade. Given that ctDNA values commonly increase in advance of radiographic progression, intuitively a change in therapy should be implemented in patients with rising values, however there is some reluctance to change therapy based on ctDNA measurement alone.

### Personalized therapy

Some of the genetic alterations described above produce cellular changes in the neoplastic cells that are potentially targetable therapeutically. For example, somatic *BRAF* mutations occur in 1–3% of pancreatic cancers, and *BRAF* mutations have proven targetable in a number of tumor types [220, 221]. In fact, the Food and Drug Administration recently approved the combination of Encorafenib and Cetuximab for metastatic colon cancer with *BRAF* mutations [220]. Furthermore, although rare, some pancreatic cancers harbor potentially targetable gene fusions [15, 222–226]. For example, pancreatic cancers with *NTRK* gene fusions have been treated with tropomyosin receptor kinase inhibitors [222, 223]. Similarly, some *KRAS* wild-type pancreatic cancers harbor somatic *NRG1* gene fusions, and some of these cancers have been reported to respond to treatment with a HER-family kinase inhibitor [225, 226].

Overall, however, although theoretically targetable genetic alterations are present in 30–40% of pancreatic cancers, the results of targeted therapies have mostly been disappointing, with, at best, mixed results [11–13, 15]. The poor track record in treating potentially targetable somatic mutations is, in part, due to the short life expectancy for many patients with pancreatic cancer. There just is not the time to sequence their cancers and develop a treatment plan based on the somatic mutations in most cases. The exceptions to this have been the targetable germline alterations described above in the sections on familial pancreatic cancer [11–13, 15]. On a positive note, the "Know Your Tumor" trial of over 1500 patients with pancreatic cancer reported an improved outcome in the patients who received targeted therapies based on the molecular profiles of their cancers [227]. Cancer centers are currently building the infrastructure needed to test cancers quickly and to efficiently institute personalized care.

The elephant in the room for targeted therapy remains KRAS [10]. After decades of investments, KRAS was deemed "undruggable" by many [10, 228, 229]. The protein lacks an efficient small-molecule binding pocket and has a high affinity for guanosine triphosphate, which is at high concentration in the cytoplasm [229]. Recently, however, several significant advances were made in targeting KRAS, especially the *KRAS* G12C alterations, and several inhibitors specifically inhibiting *KRAS* G12C are now in clinical trials [229]. Unfortunately, *KRAS* G12C mutations are only a small fraction of *KRAS* mutations in pancreatic cancers. Broader KRAS inhibitors could have real impact, as 95% of pancreatic cancers harbor *KRAS* gene mutations [191].

## Future directions

The last decade has witnessed dramatic progress, but the death rate from pancreatic cancer is still unacceptably high, and much needs to be done. Looking forward, we envision major advances in five broad areas.

First, as outlined above, the discovery of deleterious germline variants that predispose to pancreatic cancer has had enormous clinical impact. However, many individuals carry a variant of uncertain significance in a pancreatic cancer susceptibility gene, and it is unclear how these individuals should be managed [17]. In the next decade, we believe that most germline variants will be categorized into benign or deleterious, improving the clinical management of all patients. Furthermore, as the functional pathways perturbed by deleterious germline variants are defined, we envision the development of novel therapies that specifically target these pathways.

Second, we envision the development of new combinations of targeted therapies. The emergence of drug resistance when a single targeted agent is given should not be surprising. It was, in fact, entirely predictable based on previous experience treating patients with tuberculosis and treating patients infected with the human immunodeficiency virus [230]. As understanding of pancreatic cancer grows, combinations of therapies, each exploiting a unique weakness, will be developed. These combination therapies will greatly reduce the emergence of drug resistance.

Third, we predict that the next decade will witness understandings that will bring insight into why pancreatic cancer almost universally invades veins in the pancreas [202]. In so doing, it is our hope that new therapies will be developed to impede this process, thereby reducing metastases.

Fourth, we predict that early detection will reduce pancreatic cancer deaths. Early detection approaches will include more sensitive and more specific biomarkers to distinguish low-grade precursor lesions from high-grade precursor lesions, as well as novel strategies that address sampling/multifocality issues in precursor lesions [231].

Fifth, while this review has focused on recent advances in genetics, other fields, particularly imaging, have advanced in parallel. The next decade will see better integration of diverse clinical data, creating a more integrated understanding of a patient's disease. For example, CT data will be integrated with laboratory values such as blood glucose levels, and germline and somatic sequencing data (including structural variants, chromothripsis, genome doubling, etc.). As these data sets get bigger, artificial intelligence will allow for the discovery of new patterns, patterns that otherwise would not be appreciated by the human brain [232]. This is already happening in radiology, and the integration of genetics and digital pathology into deep learning algorithms is just around the corner. Parenthetically, while we view artificial intelligence as intellectually exciting, it does tear at our hearts to think that humans will become more separated from patient care.

In sum, and in short, we have come a long way, but, paraphrasing Robert Frost, we have miles to go before we sleep.

## Compliance with ethical standards

**Conflict of interest** RHH has the potential to receive royalty payments from Thrive Earlier Detection for the GNAS invention.

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