Review Article

Genetic Testing in Pancreatic Ductal Adenocarcinoma: Implications for Prevention and Treatment

Mary Linton B. Peters, MD, MS[1]; Jennifer F. Tseng, MD, MPH[2]; and Rebecca A. Miksad, MD, MPH, MMSC[1]

[1]*Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and* [2]*Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts*

ABSTRACT

Purpose: This article reviews the progress to date and future directions for investigation of germline and somatic genetic testing to inform pancreatic adenocarcinoma (PDAC) treatment, screening, and prevention strategies.

Methods: We searched PubMed to identify recent articles regarding genetic testing in pancreatic cancer, including both germline and somatic testing, and recent genome-wide association studies. References were specifically hand searched as relevant. Guidelines for testing and screening high-risk individuals were included. We searched clinicaltrials.gov to review the current landscape of active clinical trials.

Findings: Approximately 10% of PDACs are associated with an identified germline mutation. Although germline mutations may inform treatment options and identify high-risk individuals for screening in other cancers, the data on PDAC are only now emerging. For example, poly adenosine diphosphate ribose polymerase (PARP) inhibitors are under investigation for BRCA-associated PDAC. Somatic mutations have also been identified in PDAC. However, current data are limited regarding treatment for potential PDAC somatic driver mutations. Although erlotinib is used in PDAC, its use is not targeted based on a tumor marker. Many tyrosine kinase inhibitors targeted toward potential driver mutations and critical pathways are in development, including BRAF/MEK, ALK, and CDK4/6. A consensus on screening strategies for individuals at high risk for PDAC is still evolving because of the relatively low prevalence of the disease, the relative invasiveness of endoscopic procedures often used as part of screening, and the lack of a clear survival benefit.

Implications: Pancreatic cancer has been slower to move toward genomic testing, partially because of a lower prevalence of mutations and partially because of a limited effect of results on treatment choices outside a clinical trial. This is an area of active investigation, and we anticipate that there will be both preventive and therapeutic implications of driver mutations in the coming decade. (*Clin Ther.* 2016;38:1622–1635)

Key words: genetic testing, germline mutation, pancreatic ductal adenocarcinoma, somatic mutation.

INTRODUCTION

Clinical Background

Although pancreatic adenocarcinoma (PDAC) contributes more than double its incidence rate (3% of new US cancer diagnoses per year) to cancer mortality (6.9% of US cancer deaths per year),[1] most PDAC cases are not linked to identified germline mutations.[2]

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However, somatic mutations, particularly in *KRAS*, are common.[3] Other risk factors, such as cigarette smoking, diabetes mellitus, and chronic pancreatitis, have consistent links to increased incidence of pancreatic cancer but with lower relative risks than for other malignant tumors.[1,4] Interestingly, PDAC has higher incidence rates in developed countries and among African Americans.[1] Although survival has modestly improved in the past 30 years, the overall 5-year survival is still only 7.2% in 2012, up from 3.6% in 1995 and 3% in 1975. Even localized disease that may be resectable has a 5-year survival rate of only 27%.[1]

Despite decades of research on systemic therapy for advanced PDAC, only 2 combination cytotoxic chemotherapy regimens have produced a clinically meaningful survival benefit compared with single-agent gemcitabine in the first-line setting. The FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin) regimen improved survival (11.1 vs 6.8 months) and decreased degradation quality of life at 6 months (31% vs 61%) compared with gemcitabine alone.[5] The combination of nab-paclitaxel and gemcitabine also improved survival relative to gemcitabine alone (8.5 months for the combination vs 6.7 months for gemcitabine).[6] The only targeted agent approved for PDAC treatment, the oral *EGFR* inhibitor erlotinib, improved survival by approximately 10 days when added to gemcitabine (6.24 months for the combination vs 5.91 months for gemcitabine alone).[7,8] Although there may be some association with response, *EGFR* has not proven a useful clinical tool to predict a strong erlotinib response in PDAC.[9] The choice in first-line treatment for advanced PDAC is often based on the patient's performance status and the toxicity profile of the treatment regimens.

We reviewed clinicaltrials.gov seeking active clinical trials for pancreatic cancer (accessed October 26, 2015). There are at least 90 early-stage studies of investigational therapeutic agents enrolling patients with pancreatic cancer. Most of these are early-stage, exploratory studies that include patients with a broad range of solid tumors. There are 15 later-stage studies specific to pancreatic cancer, some of which evaluate the efficacy of compounds already approved for other cancers. On the basis of historical drug development success rates,[10] it is likely that only a small proportion of these agents will be approved as anticancer therapies, and fewer still will provide clinical benefit for PDAC. Improved systemic therapy for PDAC remains a critical unmet need.

Oncogenesis of PDAC

Many PDACs appear to arise from pancreatic intraepithelial neoplasia (PanIN), an intraductal precursor lesion. As shown in Figure 1, an accumulation of genetic alterations occurs on the pathway from most well-defined PanINs to invasive carcinoma, a typical oncogenic progression.[11] Genetic predisposition syndromes act to increase the risk of oncogenesis in a variety of ways, affecting DNA repair mechanisms, microsatellite stability, or mismatch repair mechanisms. *KRAS* mutations appear to be a key somatic alteration, with low rates in pancreatitis specimens and high rates in PDAC specimens. *KRAS* mutations may also be an early mutation in the PanIN pathway because it is found in 36% to 44% of low-grade PanIN samples but up to 87% of high-grade PanIN samples.[12] *CDKN2A* is another early mutation noted in PanIN lesions. Higher-grade PanIN lesions also have *SMAD4* and *p53* mutations.[13-15]

Epigenetic alterations are also noted in PDAC. Hypermethylation is often a factor in tumor suppressor gene inactivation and increases with higher-stage pancreatic neoplasia. Overexpression of micro-RNAs is also seen in a distinct pattern in neoplastic pancreatic tissue versus normal pancreatic tissue. Although there is no current clinical application for these findings, further investigation of epigenetic markers may refine our understanding of PDAC oncogenesis and identify potential treatment targets.[15,16] This article reviews the current status of germline and somatic genetic testing in PDAC, clinical applications, and future directions for investigation.

METHODS

We performed an initial PubMed search for the terms *pancreatic cancer genetics* and *pancreatic cancer genetic testing* to identify the body of research in the last 10 years in particular. We then performed specific searches for each of the key proposed germline mutations and somatic driver mutations. Society guidelines were explicitly included. We searched clinicaltrials.gov for active clinical trials in pancreatic cancer.

DISCUSSION

Testing for PDAC genetic mutations has 2 primary purposes: (1) germline testing to identify at-risk individuals and (2) somatic and germline testing to

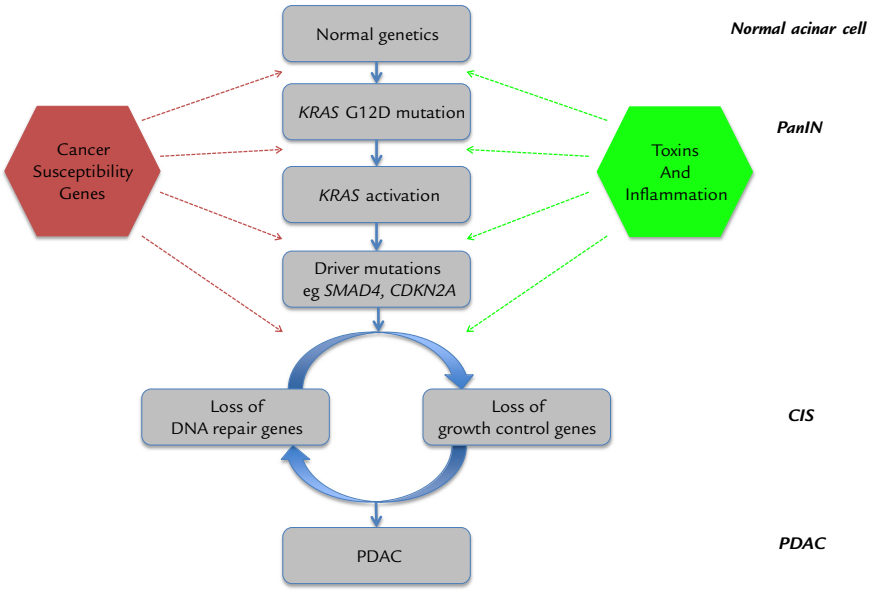

Figure 1. Pancreatic adenocarcinoma (PDAC) carcinogenesis model. Adapted from Whitcomb et al.[11] Normal acinar cells acquire somatic mutations, leading to transformation to pancreatic intraepithelial neoplasia (PanIN). Cancer susceptibility genes may play a role, but for many people this process is due to external factors, such as local toxins and inflammation. Among the first abnormalities is the *KRAS* G12D mutation, which leads to KRAS activation. Further somatic mutations are acquired, particularly *SMAD4* and *CDKN2A*, which are often seen in PDAC cells. Once dysplasia has progressed to form a carcinoma in situ, a vicious cycle of loss of DNA repair genes and loss of growth control genes leads to formation of PDAC. CIS = carcinoma in situ.

identify potential targets for treatment. Historically, routine PDAC germline testing has been hindered by an unclear definition of the target population of at-risk individuals and the absence of proven low-risk screening strategies. For example, PDAC is not included in the Amsterdam or Bethesda guidelines that define Lynch syndrome even though these individuals have a higher PDAC risk than the general population.[17,18] Similarly, the role of PDAC screening for *BRCA* carriers remains unclear, despite increased rates of PDAC and clear screening guidelines for other BRCA-associated malignant tumors.[19]

Patients with an established germline mutation that places them at risk for PDAC often undergo screening with magnetic resonance imaging (MRI) or endoscopic ultrasonography (EUS). In addition, future possible preventive approaches could include therapeutics (cyclo-oxygenase [COX] 2 inhibitors, aspirin, metformin, angiotensin-converting enzyme inhibition, or angiotensin II receptor blockade) or even prophylactic pancreatectomy. For patients with an established diagnosis of PDAC, the presence of a germline mutation may indicate susceptibility to specific chemotherapeutic agents (eg, poly adenosine diphosphate ribose polymerase [PARP] inhibitor use in patients with *BRCA*) or increased risk associated with certain treatment modalities (eg, radiation therapy in Li Fraumeni syndrome). Pharmacogenomics is being studied to optimize irinotecan dosing in the commonly used FOLFIRI regimen. Somatic mutations are increasingly in use to target chemotherapeutic approaches to driver mutation pathways, such as *HER-2*, *EGFR*, *BRAF/MEK*, and *PI3K*. microsatellite instability (MSI) high status of the tumor may indicate susceptibility to Programmed cell death protein 1 (PD-1) or other immune checkpoint inhibition. Although most of these uses are still investigational, these pathways have proven fruitful in other malignant tumors. As more is learned about the pathogenesis of PDAC, information about germline and somatic mutations may provide

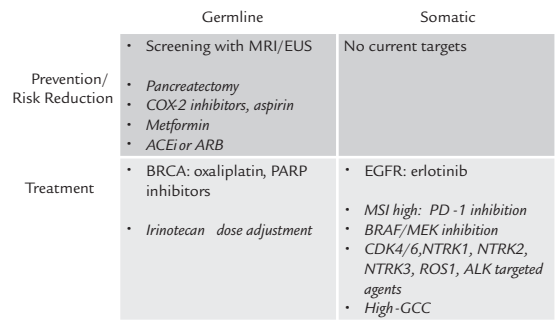

Figure 2. Types of genetic testing in pancreatic adenocarcinoma (PDAC) and implications for management. Items in italics are currently investigational. ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; COX = cyclo-oxygenase; EUS = endoscopic ultrasonography; GCC = guanylyl cyclase C; MRI = magnetic resonance imaging; MSI = microsatellite instability; PARP = poly adenosine diphosphate ribose polymerase.

	Prevalence in all pancreatic cancer patients (unselected)	Prevalence in patients with family history of PDAC	Risk of PDAC if positive
APC		< 5%	1.7%
ATM	0.9%–1%	2.4%	
BRCA1	0.4%–1%	1.2–2.6%	1.3–3.6%
BRCA2	0.7%–4%	2.9–17%	4.5–5%
CDKN2A		2.5–21%	10–28%
EPCAM			3.7–13.9%
MLH1	0.4%	2.8%	
MSH2	0.7%	5.5%	
MSH6	0.4%	2.8%	
PALB2	3.0%	0.6–3.7%	
PMS2			3.7–13.9%
STK11			11–36%
TP53	0.4%		9.5%

Figure 3. Identified germline mutations associated with pancreatic adenocarcinoma (PDAC).[19,23,25,28,31,32,33-52]

important data to individualize and optimize treatment and screening strategies (Figure 2).

Germline PDAC Mutations

During the 1970s and 1980s, multiple families were identified with a clear pattern of heritable PDAC.[20,21] A recent observational study comparing 370 familial PDAC kindreds to 468 sporadic PDAC kindreds found a 32-fold increased risk of PDAC in those families with at least 3 affected members.[22] With the advent of advanced sequencing techniques, the causative germline mutation for some PDAC pedigrees was established in the mid-1990s: *BRCA1*,[19,23] *HNPCC* genes,[24] familial atypical multiple mole melanoma (FAMMM)/*CDKN2A*,[25] and Lynch syndrome[24] genes (*EPCAM, MLH1, MSH2, MSH6,* and *PMS2*).

In studies of roughly 1500 patients with PDAC with a positive family history referred for genetic testing by a variety of criteria, approximately 10% to 12% of patients have been found to have a germline mutation.[2,26] Specific target genes include *APC*, *BRCA1* and *BRCA2*, *CDKN2A*, the Lynch syndrome genes (*EPCAM, MLH1, MSH2, MSH6,* and *PMS2*), *STK11*, and *TP53*. Several commercial PDAC panels also include *ATM*, *PALB2*, and *SPINK1*. In the studies of patients with PDAC with high-risk family histories, the most commonly found mutations are *BRCA2* (2.9%–17%), *CDKN2A* (2.5%–21%), and the Lynch genes (11%).[27–30] A summary of these studies appears in Figure 3.

However, several studies have questioned the overall prevalence of these germline mutations among unselected patients with PDAC. One retrospective study of 290 patients with newly diagnosed PDAC in Ontario found an overall mutation prevalence of 3.8% (*ATM*, *BRCA1*, *BRCA2*, Lynch genes, *TP53*).[53] A prospective study of 306 patients with newly diagnosed PDAC found 1% with *BRCA1* mutations and 3.6% with *BRCA2* mutations.[31]

Recent American College of Medical Genetics and Genomics guidelines recommend genetic testing referral for patients with PDAC of Ashkenazi Jewish heritage, multiple relatives affected by PDAC, or those patients with risk factors for Lynch syndrome, Peutz-Jeghers syndrome, or FAMMM.[26] The American College of Gastroenterology (ACG) released similar genetic testing guidelines for PDAC patients with a suspicious family history.[32] A summary of these guidelines can be found in Figure 4. Although germline testing for patients with PDAC with a high-risk family history has been endorsed, current knowledge is limited about the clinical utility of the information for the patient and the best practices for testing and screening of the patient's family members.

We review the specific evidence linking each of the 14 most commonly cited genetic mutations to the development of PDAC in the following sections.

		American College of Medical Genetics and Genomics (ACMG)	American College of Gastroenterology (ACG)
Heritage		Ashkenazi Jewish heritage (BRCA testing only)	N/A
Family History		≥ 2 cases of PDAC in close relatives (BRCA testing only)	• ≥ 2 relatives with PDAC, where one is a first degree relative • ≥ 3 relatives with PDAC
Co-morbidities		N/A	History of hereditary pancreatitis
Cancer Syndromes	BRCA	≥ 2 cases of breast, ovarian, and/or aggressive prostate cancer in close relatives	N/A
	Lynch	PDAC and 2 other cases of any Lynch syndrome-associated cancer in the same person or close relatives	Evaluation for Peutz-Jeghers, Lynch, and hereditary pancreatitis genes should be considered if personal and/or family history criteria are met for the syndrome
	Peutz-Jegher	PDAC and ≥ 1 Peutz-Jegherpolyp in the same person	
	FAMMM	• 3 cases of PDAC and/or melanoma in close relatives • PDAC and melanoma in the same person	
Other			Testing should include analysis of BRCA 1 and 2, CDKN2A, PALB2, and ATM

Figure 4. Comparative summary of guidelines for pancreatic adenocarcinoma (PDAC) genetic testing.[26,32] FAMMM = familial atypical multiple mole melanoma; N/A = not applicable.

APC *Gene (Familial Adenomatous Polyposis)*

The *APC* gene on 5q is part of the Wnt signaling pathway, acting as a tumor suppressor via its action on β-catenin.[54] Germline mutation in *APC* leads to familial adenomatous polyposis, which is strongly associated with colon cancer. A retrospective review of 197 familial adenomatous polyposis kindreds revealed a slightly increased risk of PDAC.[33] Given the small magnitude of added risk, the ACG 2015 guidelines do not recommend *APC* testing for patients with PDAC.[32]

ATM *Gene (Ataxia-telangiectasia syndrome)*

ATM on 11q is involved in repair of DNA double-strand breaks. Mutations in *ATM* are associated with ataxia-telangiectasia syndrome and have also been implicated in some familial cancers. *ATM* mutation was initially identified as a possible cause of non-*BRCA* familial breast cancer,[34] and recent studies have found that *ATM*-associated prostate cancer may respond to PARP inhibition.[35] *ATM* is present in some pancreatic cancer lineages, with uncertain effects on the risk of developing this malignant tumor.[36]

BRCA1, BRCA2, *and* PALB2 *Genes (Hereditary Breast and Ovarian Cancer)*

BRCA1 (17q) and *BRCA2* (13q) are widely studied DNA repair genes initially identified because of their association with familial breast and ovarian cancer. In addition, *BRCA* carriers have a higher than population risk of gastric, prostate, colon, skin (melanoma), and pancreatic cancers, as well as increased risk of hematologic malignant tumors.[37] The risk of pancreatic cancer in *BRCA1* and *BRCA2* carriers has been specifically noted in Ashkenazi Jewish families.[38] Population studies of *BRCA* carriers indicate a 2- to 4-fold increased risk of pancreatic cancer among carriers,[19,23] with higher risk accorded to *BRCA2* mutations versus *BRCA1* in most studies.[31,39,40] *PALB2* is found on 16p and also interferes with DNA repair in partnership with *BRCA2*. The exact role of *PALB2* in pancreatic cancer development has not been elucidated; however, *PALB2*-deficient patients are sensitive to PARP inhibitor therapy.[41] The ACG recommends screening only for patients with a proven mutation and a first- or second-degree relative with pancreatic cancer but notes a low quality of evidence.[32]

CDKN2A *Gene (p16, Familial Atypical Multiple Mole Melanoma)*

Mutations in the *CDKN2A* gene on 9p cause FAMMM syndrome. In 2002, Lynch et al[42] identified a cohort of 8 families with FAMMM and *CDKN2A* mutations who also had increased risk of pancreatic cancer. Germline mutations have been found in multiple studies to cause a significant increase in pancreatic cancer risk, ranging from 10- to 15-fold.[25,28,40,43-46] However, as noted in several of these studies, there is wide variance in PDAC incidence across families.

MLH1, MSH2, MSH6, PMS2, *and* EPCAM *Genes (Lynch syndrome)*

Germline mutations in this family of DNA mismatch repair genes led to Lynch syndrome, one of the earliest identified gastrointestinal cancer syndromes and one of the first genetic cancer predisposition syndromes to be linked to pancreatic cancer. Germline mutations in this family of DNA mismatch repair genes can lead to predisposition to multiple tumors: colon, endometrial, ovarian, small bowel, gastric, breast, prostate, and genitourinary tract. This leads to a 20% to 70% lifetime risk of colon cancer, 15% to 45% lifetime risk of endometrial cancer, and 2% to 10% lifetime risk of ovarian cancer.[55] The increased risk of pancreatic cancer in patients with Lynch syndrome is estimated at a 3- to 10-fold population risk.[47] However, the most recent ACG guidelines do not recommend enhanced screening for pancreatic, prostate, or breast cancer in patients with Lynch syndrome.[32]

SPINK1 *Gene (Hereditary pancreatitis)*

The *SPINK* genes encode inhibitors that protect the pancreas from inappropriate activation of trypsin. Mutation in *SPINK1* on 5p can lead to both acute and chronic pancreatitis, particularly in the presence of alcohol consumption. Because chronic pancreatitis has been put forward as a risk factor for pancreatic cancer, *SPINK1* has been investigated as a possible oncogene.[48] However, the population prevalence of *SPINK1* is not well characterized, and one recent study did not find a correlation between pancreatic cancer and *SPINK1* mutation.[49]

STK11 *Gene (Peutz-Jeghers syndrome)*

STK11 on chromosome 19 is a tumor suppressor gene that, when mutated, leads to an autosomal dominant hamartomatous polyposis of the intestine (Peutz-Jeghers syndrome). The lifetime cancer risk for patients with Peutz-Jeghers syndrome is high for colon, breast, cervical, lung, liver, endometrial, and pancreatic cancers. The relative risk of PDAC is 10- to 20-fold, and patients with Peutz-Jeghers syndrome tend to have the condition diagnosed at a much younger mean age.[40,50,51] Thus, the ACG recommends surveillance with EUS or MRI starting at the age of 35 years but notes a low quality of evidence.[32]

p53 *Gene (Li Fraumeni syndrome)*

The *p53* tumor suppressor gene on 17p is a common somatic mutation in many different malignant tumors. As a germline mutation, it leads to the Li Fraumeni syndrome, a rare but devastating condition. Patients with germline *p53* mutations are susceptible to multiple, early, aggressive cancers, including sarcomas, adrenal carcinomas, leukemias, and lung cancer. Many other malignant tumors have been found in Li Fraumeni kindreds, including pancreatic cancer.[52]

Somatic Mutations

The number of somatic mutations observed in each type of malignant tumors ranges broadly. Pancreatic ductal adenocarcinoma sits in the middle of this spectrum, with roughly 100 to 150 somatic mutations found in each tested specimen.[56] Of these, almost all PDAC specimens have mutation in the *KRAS* oncogene. Other common findings are *p53*, *CDKN2A* (35%), and *SMAD4* (31%-55%). In some cases, *p53* and *SMAD4* mutations were found in later-stage tumors and metastatic sites rather than in the initial primary.[57] Many other somatic mutations were identified in 5% to 10% of tested tumors, including *ARID1A, ROBO2, KDM6A, PREX2, RNF43, EphA2, SHH*, and *INK4A/ARF*.[57–60] *SMAD4* is unique because this tumor suppressor is not often mutated in other tumor types.[14]

A recent genome-wide association study of unselected pancreatic adenocarcinomas from patients with no family history or other known high-risk features found a low rate of common targetable mutations. *ERBB2, MET, FGFR1, CKD6, PIK3CA*, and *BRAF* were all identified in only 1% to 2% of tested tumors. Somatic *BRCA1* mutations were noted in 3% of tested tumors and *BRCA2* in 2%.[58] Although a moderate number of somatic mutations are found in pancreatic adenocarcinomas, most are not currently

actionable with targeted therapy such as tyrosine kinase inhibitors.

KRAS *Gene*

Almost all PDAC specimens have mutations in the *KRAS* oncogene. In colorectal cancer, mutations in *KRAS* have been associated with a significant reduction in overall survival and have a lower response to *EGFR*-targeted therapy.[61–64] In PDAC samples, *KRAS* positivity has also been associated with poor prognosis.[65] National Comprehensive Cancer Network© (NCCN©) guidelines now include a recommendation for *KRAS* and *NRAS* testing for stage IV colorectal cancers, which has therapeutic implications.[66] Similar testing recommendations may in the future be recommended for PDAC. Unfortunately, *KRAS* is not currently directly targetable by drug therapy.

BRCA *Gene*

Somatic mutations in *BRCA1* and *BRCA2* are common in ovarian cancer, and *BRCA*-deficient ovarian tumors, whether due to germline or somatic mutation, respond equally well to platinum-based chemotherapy.[67] A recent review concludes that *BRCA* mutation is a marker for genetic instability in PDAC and that PARP inhibitors and platinum-based chemotherapy can be effective in this setting as in other tumor types.[68]

MSI

MSI is due to poor DNA mismatch repair and is a critical factor in the treatment of colorectal cancers in particular.[69] MSI-high patients with colon cancer have a favorable prognosis relative to those with intact mismatch repair.[70] Some studies have found reduced efficacy of fluoropyrimidine-based therapy in MSI-high colorectal cancers.[70,71] Recently, MSI has emerged as a potential marker for the efficacy of PD-1 blockade in gastrointestinal malignant tumors. A recent Phase II study found a substantially higher response rate to PD-1 inhibition among MSI-high colorectal cancers.[72] The same group has expanded their work into noncolorectal gastrointestinal tumors, and preliminary results presented at the recent American Society of Clinical Oncology Gastrointestinal Cancers Symposium revealed similarly promising results.[73] Although MSI testing is not currently standard in pancreatic cancer, it is emerging in research settings.

IMPLICATIONS FOR TREATMENT

Germline Mutations

BRCA1, BRCA2, and PALB2

Emerging evidence suggests *BRCA1*- and *BRCA2*-associated PDACs may respond more briskly to platinum-based therapy. In a recent retrospective review of patients with stage III or IV disease, those treated with platinum-based chemotherapy (n = 22) had a significantly longer overall survival (22 vs 9 months, $p < 0.039$) than those treated without platinum chemotherapy (n = 21).[74] The results of similar studies in breast and ovarian cancers have been inconsistent but have revealed an overall trend toward improved survival with platinum use.[75,76]

In patients with deficiencies in double-strand repair (due to *BRCA1*, *BRCA2*, or *PALB2* mutations), PARP inhibitors have substantial efficacy.[41] PARP is responsible for the repair of single-strand DNA breaks, and PARP inhibitors block single-strand repair in rapidly dividing tumor cells. In late 2014, olaparib was approved for use in advanced ovarian cancer in patients with germline *BRCA* mutations.[77] Currently, multiple PARP inhibitors are in development in a variety of *BRCA*-associated tumors, and several Phase II and III studies are currently recruiting in pancreatic cancer specifically (NCT02184195, NCT01989546, NCT02286687, NCT01489865, NCT01585805).

Pharmacogenomics

Currently, 2 clinical trials are under way on the use of *UGT1A1* gene polymorphism testing to dose adjust irinotecan in the FOLFIRINOX regimen used to treat PDAC (NCT02143219, NCT01643499). Similar studies have evaluated this approach for FOLFIRI regimens used in colorectal cancer. Irinotecan can cause neutropenia and delayed diarrhea in some patients. One proposed mechanism for this toxic effect is polymorphisms of the *UGT1A1* gene, which is part of the glucoronidation pathway of metabolism. Polymorphisms in *UGT1A1,* such as the *28 allele, are associated with Gilbert syndrome, and absence of the enzyme leads to Crigler-Najjar syndrome, both disorders of bilirubin glucoronidation.[78] The association of irinotecan toxicity with *UGT1A1* polymorphisms was first noted in a Japanese population, and further studies in Asian populations have found a correlation between *UGT1A1* polymorphisms and these adverse effects.[79–82] However, these polymorphisms

are present in all ethnic groups. Pharmacogenomic studies have found a correlation between irinotecan-associated neutropenia and the same *28 allele implicated in Gilbert syndrome.[83] This allele is present in all ethnic groups and is in fact more common in white than in Asian populations.

A case series of 48 patients receiving gemcitabine monotherapy revealed that a single-nucleotide polymorphism in the *MDR1* gene correlated with increased adverse effects but also with longer disease-free survival. This finding was thought to indicate higher drug levels in this population with *MDR1* 2677 mutation. This *MDR* polymorphism has not been further investigated for clinical use.[84]

Somatic Mutations

Similar to other gastrointestinal malignant tumors, most of the somatic mutations found in PDAC are not currently targetable. Future treatment approaches that target common mutations, such as *CDKN2A* or *SMAD4*, could have significant application.

KRAS *Gene*

KRAS is present almost universally in PDAC but is not a currently targetable mutation. *KRAS* mutation is associated with poor prognosis in both resected and advanced tumor samples.[65] Investigation of the *KRAS* oncogenic pathway reveals several downstream targets that may prove more amenable to intervention, particularly the *RAF/MEK/ERK* and *PI3K/PDK1/AKT* pathways.[85,86] *RAF/MEK* inhibition is being tested in colorectal cancer among *KRAS* mutated tumors as an approach for treating *EGFR*-insensitive metastatic disease (NCT02450656, NCT02278133, NCT02230553). In pancreatic cancer, there are currently open Phase I/II studies of several targeted therapies, with evidence largely drawn from the colorectal cancer experience. *RAF/MEK* inhibitors are being studied in pancreatic cancer, also with the assumption of *KRAS* mutation presence (NCT02039336, NCT02230553, NCT02243917, NCT01449058).

The *EGFR* inhibitor erlotinib has a small survival benefit in combination with gemcitabine in pancreatic cancer. In a Phase III study, patients had increased overall survival of 2 weeks in the erlotinib group (6.24 vs 5.91 months) and an increased rate of survival at 1 year (23% vs 17%).[7] Similar studies with cetuximab did not find any increased survival, and only erlotinib is approved for use in pancreatic cancer in combination with gemcitabine. However, these studies did not stratify patients by serologic or tumor markers.

MSI

Colorectal cancers with impaired mismatch repair leading to MSI-high status have better prognosis than those with preserved mismatch repair. Recent studies in PD-1 inhibition reveal particular promise in the MSI-high subset of colorectal tumors. A Phase II study is under way in noncolorectal gastrointestinal tumors, including pancreatic cancer. Early results from the first 17 patients, 4 of them with pancreatic cancer, indicate an overall response rate of 50%.[73] This study continues enrollment with a goal of an additional 50 patients (NCT 01876511).

Others

There are open studies for *BRAF, CDK4/6, NTRK1, NTRK2, NTRK3, ROS1*, and *ALK* mutated tumors, many of these in "basket" studies that recruit across multiple solid tumors (NCT01351103, NCT02187783, NCT02568267, NCT02097810). Both lapatinib and the investigational agent AVX901 are being tested in the rare *HER2* overexpressed pancreatic tumors as part of larger solid tumor studies. Finally, the investigational antibody-drug conjugate MLN0264 that targets high guanylyl cyclase C–expressing tumor cells is being developed specifically for PDAC (NCT02202785). Given the relatively low prevalence of some of these driver mutations among pancreatic tumors tested to date, it is not clear how broadly applicable these approaches may be in future. A summary of open clinical studies can be found in Figure 5.

IMPLICATIONS FOR PREVENTION

Germline Mutations

Screening

The Cancer of the Pancreas Screening Consortium was formed in 2010 to address the question of who should be screened for pancreatic cancer and how this screening should be performed. The goal of these studies is to identify carcinoma in situ and early-stage invasive cancers that can be resected with a reasonable chance of cure. The 2013 Cancer of the Pancreas Screening guidelines recommend screening via EUS or MRI starting at the age of 50 years for high-risk individuals. High risk is defined as patients with an

Stratified by germline mutation				Clinicaltrials.gov #
Phase III	olaparib	PARP inhibitor	BRCA 1/2	NCT02184195
Phase II	BMN 673	PARP inhibitor	BRCA 1/2	NCT01989546, NCT02286687
Phase II	velibarib (ABT888)	PARP inhibitor	BRCA 1/2 or PALB2	NCT01489865, NCT01585805
Phase I/II	irinotecan dose adjustment		UGT1A1 level (Dose adjustment by expression profile)	NCT02143219, NCT01643499
Stratified by somatic mutation / marker				
Phase I/II	dacomitinib + PD-0325901	EGFR and MEK	KRAS mutated	NCT02039336
Phase I/II	lapatinib + trametinib	HER-2/EGFR and MEK	KRAS mutated, PIK3CA wildtype	NCT02230553
Phase I	CB-5083	p97	KRAS mutated	NCT02243917
Phase I	BYL719 + MEK162	PI2K and MEK	RAS or BRAF mutated	NCT01449058
Phase I	LGK974	PORCN/Wnt	BRAF mutated	NCT01351103
Phase II	LEE011	CDK 4/6	CDK 4/6 positive	NCT02187783
Phase I	entrectinib (RXDX-01)	pan-trk, ROS1, ALK	NTRK1, NTRK2, NTRK3, ROS1, ALK mutation	NCT02568267, NCT02097810
Phase II	lapatinib	HER-2/EGFR	HER2 overexpressed	NCT02342587
Phase I	AVX901	HER-2 vaccine	HER2 overexpressed	NCT01526473
Phase II	MLN0264	antibody-drug conjugate GCC	GCC high	NCT02202785

Figure 5. Investigational treatments for pancreatic adenocarcinoma (PDAC). GCC = guanylyl cyclase C.

identified germline *BRCA2*, *CDKN2A*, *APC*, or *STK11* mutation and a first-degree family member with PDAC. Individuals without a known germline mutation are recommended for screening if they have ≥2 relatives, with at least 1 a first-degree relative, affected by pancreatic cancer.[2]

A German national cancer registry applied a similar screening program for 76 high-risk individuals with familial cancer syndromes. These individuals underwent annual EUS and MRI screening for 5 years. Twenty-eight patients had some abnormality by noninvasive imaging, for which 7 fine-needle aspirations were performed and 7 laparoscopies were completed, 6 with limited resections. Pathologic examination revealed 3 adenomas, 1 intraductal papillary mucinous neoplasm (IPMN), and 4 low-intermediate PanINs. PanINs are generally thought to have a low risk of progressing to cancer. Only the individual with IPMN had a lesion with a clear high risk of future pancreatic adenocarcinoma. The authors concluded that the yield of this extensive screening program was low and that it did not justify the significant cost and patient distress incurred.[87]

A similar screening program was recently tested in Sweden, in which 40 individuals with increased risk of pancreatic cancer were identified based on family history (≥2 relatives with PDAC). All patients underwent genetic testing for *BRCA* and *CDKN2A*, identifying 1 with a *BRCA1* mutation, 2 with a *BRCA2* mutation, and 4 with a *CDKN2A* mutation. The patients underwent MRI or magnetic resonance cholangiopancreatography, followed by EUS with biopsy or computed tomography if any suspicious lesions were noted on initial imaging. Sixteen patients had a positive finding, of which 14 were IPMNs and 2 were PDACs. Five patients underwent resection, 3 of whom were found to have early-stage PDAC. In 1 of these 3 patients, the PDAC was found in the surgical specimen but not noted on imaging. This study concluded that in this high-risk population MRI screening could identify early lesions with good accuracy and with lower risk to the patient than strategies that include regular EUS use.[88]

For individuals with *BRCA* mutations, NCCN guidelines recommend annual breast MRI and mammography, possible prophylactic mastectomy and salpingo-oophorectomy, prostate cancer screening for men, and symptom-based screening for other malignant tumors. There is no specific NCCN guideline for skin examination, pancreatic cancer screening, or other malignant tumors, although some institutions may have more specific recommendations. The NCCN recommends that individuals with identified *p53* mutations undergo annual whole-body MRI, skin examination, mammography, and symptom-targeted surveillance, as well as colonoscopy every 2 to 5 years. Although pancreatic cancer screening is not specified, the whole-body MRI may be adequate to assess for PDAC.[89] A summary of screening guidelines can be found in Figure 6.

Chemoprevention

There are no proven interventions to reduce the risk of developing PDAC other than standard healthy lifestyle choices recommend for general cancer prevention. However, there are several medications that

		International Cancer of the Pancreas Screening (CAPS) Consortium	American College of Gastroenterology (ACG)	National Comprehensive Cancer Network® (NCCN®)
Family History		• ≥ 3 close relatives (at least 1 first degree) with PDAC • ≥ 2 first degree relatives with PDAC • Start age 50, Q1-2Y EUS or MRI	• Start age 50, Q1Y, EUS or MRI or MRCP	
Cancer Syndromes	BRCA	• ≥1 first degree relative with PDAC • ≥ 2 close relatives with PDAC • Start age 50, Q1-2Y EUS or MRI		
	Lynch	• ≥ 1 first degree relative with PDAC • Start age 50, Q1-2Y EUS or MRI	• ≥ 1 FDR • Startage 50, Q1-2Y EUS or MRI	
	Peutz-Jegher	• All patients • Start younger, Q1-2Y EUS or MRI	• All patients • Start age 30, Q1-2Y EUS or MRCP	• All patients • Start age 30-35, Q1-2Y EUS or MRCP
	Li Fraumeni			• Annual whole body MRI
	FAMMM			

Figure 6. Comparative summary of selected screening strategy recommendations.[2,32,66,89,90] EUS = endoscopic ultrasonography; FAMMM = familial atypical multiple mole melanoma; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; NCCN © = National Comprehensive Cancer Network ©; PDAC = pancreatic adenocarcinoma.

have preclinical and in vitro data indicative of potential application in risk reduction, and future research may identify those germline mutations most likely to benefit from these measures.

Metformin

For patients with pancreatic cancer, there are dozens of active clinical trials testing metformin in combination with traditional chemotherapy. A recent meta-analysis found that metformin use reduced the risk of pancreatic cancer among diabetic patients (relative risk, 0.63).[91] Metformin is being tested as a possible means to reduce the risk of breast cancer and hepatocellular carcinoma among patients with obesity or impaired glucose tolerance (NCT02028221, NCT02319200).

Angiotensin Receptor Blockers

Similarly, angiotensin II receptor blockers have a beneficial effect in combination with traditional chemotherapy.[92,93] In vitro models have revealed that blocking the renin-angiotensin system reduces the proliferation of pancreatic cancer cells.[94] Losartan is being studied in combination with FOLFIRINOX (NCT01821729), but there are no active prevention studies at this time.

COX-2 inhibitors

COX-2 inhibition has also been mooted as a potential mechanism for in vitro suppression of tumor growth.[95] Although celecoxib has been tested in combination with chemotherapeutics in early-stage clinical trials, concern about long-term toxic effects has limited its use.

Aspirin

Aspirin reduces the development of adenomatous polyps and colon cancer.[96] This reduction may be due to irreversible COX-2 inhibition or to anti-inflammatory effects. It is not currently recommended for regular use for this purpose because of the risk of gastrointestinal bleeding in particular, although a recent Agency for Healthcare Research and Quality decision analysis found benefit in younger adults with limited bleeding risk.[97,98] Retrospective analysis has also found a benefit for aspirin in the prevention of PDAC, although given the lower prevalence of PDAC relative to colorectal cancer, the overall risk-benefit for its use in this setting is likely to be lower as well.[99]

Somatic Mutations

For patients with newly diagnosed PDAC, it would be ideal to identify adjunct treatments that could reduce metastatic potential. Despite the therapeutic potential of small molecule tyrosine kinase inhibitors, patients with PDAC treated with these therapies all eventually have disease progression. In addition, the substantial overall survival and disease-free survival benefit of targeted therapies and immunotherapies seen for many cancers has not yet been found in PDAC. Erlotinib, an *EGFR* inhibitor approved for use in pancreatic cancer in combination with standard chemotherapy, provides only a small benefit and is not targeted to any particular subpopulation based on tumor or serologic markers. This remains an area of investigation.

CONCLUSIONS

Genetic testing has become a key component of oncology care for multiple tumor types. Pancreatic cancer has been slower to move toward genomic testing, partially because of a lower prevalence of mutations and partially because of the limited effect on treatment choices outside a clinical trial. A consensus on screening strategies for individuals at high risk for PDAC is still evolving because of the relatively low prevalence of the disease, the relative invasiveness of endoscopic procedures often used as part of screening, and the lack of a clear survival benefit. Although somatic driver mutations have been identified for PDAC, particularly *KRAS*, effective targeted treatments are not currently available. However, we anticipate that in the near future there will be therapeutic implications of some genetic mutations, particularly PARP inhibitors for patients with *BRCA* and *PALB*. We also anticipate that the growth of targeted therapies will yield treatments for PDAC driver mutations in the next 5 to 10 years. With these changes, the value of genetic testing in pancreatic adenocarcinoma will increase. Investigation of PDAC mutations and their implications for management of patients and high-risk individuals will be a key strategy to improve detection and treatment of this aggressive malignant tumor.

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Address correspondence to: Mary Linton B. Peters, MD, MS, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Shapiro 913, 330 Brookline Ave, Boston, MA 02215. E-mail: mbpeters@bidmc.harvard.edu