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Genetics in Gastroenterology Practice (B Katona, Section Editor)

Pancreatic Cancer Surveillance: Who, When, and How

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Abstract

Purpose of Review Individuals who have an increased risk for pancreatic cancer (PC) due to personal or family history may benefit from surveillance of the pancreas to increase the likelihood of early detection. This review explores current indications for PC surveillance, as well as options for surveillance modality and timing, and data regarding surveillance outcomes.
Recent Findings Recently published data suggests that individuals undergoing surveillance who develop PC are more likely to be diagnosed with resectable disease, which improves survival. Several professional organizations have published guidelines for surveillance to help define who should have surveillance, when surveillance should be performed, and how it can be accomplished.
Summary PC surveillance should be considered for individuals with a pathogenic variant in a PC-related gene who have an affected first- or second-degree relative and for individuals in a familial pancreatic cancer family who have an affected first-degree relative. Surveillance should begin at age 50, or 10 years before the earliest age of PC diagnosis in the family. Endoscopic ultrasound (EUS) or MRI/MRCP are both reasonable surveillance options, but EUS may be better at detecting small solid changes in the pancreas. Ideally, surveillance should be performed at expert centers in conjunction with research protocols.

Introduction

Pancreatic adenocarcinoma (PC) accounts for approximately 3% of cancer diagnoses in the USA but is responsible for 7.5% of all cancer-related deaths [1]. Poor survival is due in part to the fact that most

individuals are diagnosed at a late stage. The overall 5-year survival rate for PC is 9.3%; individuals with localized disease have a vastly better 5-year survival (37.4%) than individuals with regional (12.4%) or distant (2.9%) disease [2•]. Localized disease, however, only represents 10% of all PC cases, whereas over half of individuals present with metastatic disease at the time of diagnosis [2•]. Improved early detection, then, has the potential to increase survival if one can diagnose PC at a stage when the tumor is small and limited to the pancreas. Identifying appropriate candidates for PC surveillance and determining when and how they should be evaluated is an important public health issue.

Since 2013, three major organizations have published recommendations that address the questions of who, when, and how for PC surveillance. In 2013, the International Cancer of the Pancreas Screening (CAPS) Consortium published their consensus statement on surveillance and management of high-risk individuals with an inherited predisposition to PC [2•]. In 2015, the American College of Gastroenterology (ACG) published a clinical guideline regarding management of hereditary gastrointestinal cancer syndromes [3••]. In 2019, the American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion regarding genetic susceptibility to PC [4•]. Here, we review these recommendations, as well as other literature regarding this topic.

Pancreatic Cancer Surveillance: Who?

The lifetime risk for PC in the US general population is 1.6% [1]. Screening for PC in the general population is not feasible because of the large number of false positives due to the disease's rarity. To illustrate this point, one can use the age-adjusted annual PC incidence rate of 12.9 per 100,000 individuals [1] and utilize a theoretical biomarker with almost perfect performance characteristics of 100% sensitivity and 99% specificity. If this biomarker was applied to 100,000 individuals, all 13 cases would be detected; however, ~ 1,000 false positive cases would be identified. Thus, it is not possible to screen the general population, and current efforts are focused on the identification of an enriched population that is at high-risk for developing PC.

Although this group of individuals is not the focus of our review, the most common reason that individuals begin PC surveillance is to monitor pre-malignant pancreatic cysts, which are often incidentally found through imaging performed for other reasons. Based on autopsy and imaging studies, it has been estimated that millions of individuals in the USA have a pancreatic cyst and that the majority of these are small side branch IPMNs [5, 6, 7]. It is important to recognize that individuals with IPMNs are not only at risk for PC arising from a cystic lesion but also elsewhere in the pancreas through the PanIN pathway. Studies have suggested that these concomitant PC may occur at a rate of 1% per year in patients with known IPMN [5, 8]. The management of these cysts is greatly debated and has been the focus of multiple recent guidelines [7, 9, 10]. At our institution, we typically utilize the revised Fukuoka guidelines but incorporate cyst fluid analysis in those patients with incidental cystic lesions that are 15 mm or greater in size [11, 12].

The other primary reason that individuals undergo PC surveillance is because they have an increased risk for the disease based on an identified genetic predisposition and/or a family history of PC. This group is the primary focus of our review.

Currently, 13 cancer susceptibility genes are known to be associated with an increased risk for PC [13–22]. Each of these genes is primarily associated with

increased risks for other types of cancer, and their influence on PC risk is variable. Pathogenic variants in PRSS1, which cause hereditary pancreatitis, also increase risk for pancreatic cancer but have not been associated with other cancer types [23]. See Table 1 for more information about these genes.

The identification of individuals who have pathogenic variants (PV) in a PC-susceptibility gene has ballooned over the past 5 years due to the availability of multi-gene panel testing. Recently, several organizations, including National Comprehensive Cancer Network (NCCN) [24] and ASCO [4•], have issued guidelines that advocate genetic testing for any individual with PC after multiple publications reported that 3–10% of unselected individuals are found to have an actionable PV through multi-gene panel testing [25–29]. As universal genetic testing for individuals with PC increases, the number of unaffected family members who are found to carry the known familial PV through cascade testing will also grow. Likewise, the number of individuals without cancer who undergo genetic testing because they have a family history of PC will continue to increase. Understanding appropriate surveillance options for these individuals is therefore of increasing importance to the clinicians who care for them.

As shown in Table 1, the magnitude of PC risk conferred by a PV varies by gene. This variability has been taken into account in determining recommendations for surveillance candidates. For genes that are associated with substantial PC risk, surveillance may be recommended regardless of whether or not an individual has a family history of PC. For PC susceptibility genes that confer a more modest impact on risk, it has been suggested that PC risk is more significant for PV carriers who have a family history of PC than those who do not [5, 30]. As such, recommendations for surveillance have been limited to individuals who have a family history of PC.

Most individuals with PC who undergo genetic testing will not have a PV identified. Many of these individuals likely developed sporadic disease, perhaps due to lifestyle or environmental risk factors, but some individuals may have undetectable genetic factors that contribute to their diagnosis. Clinical concern

Table 1. Genes associated with pancreatic cancer risk

Gene (syndrome)	Risk for developing PDAC	Other associated cancers
APC [13] (familial adenomatous polyposis)	Up to 5-fold	Colon, upper GI, thyroid, brain
ATM [14, 15]	3-fold	Breast
BRCA1/BRCA2 [16, 17] (hereditary breast and ovarian cancer)	2- to 9-fold	Breast, ovary, prostate, melanoma
CDKN2A [18](familial atypical multiple mole melanoma)	13-fold	Melanoma
MLH1, MSH2, MSH6, PMS2, EPCAM [19] (Lynch syndrome)	9-fold	Colon, uterine, upper GI, ovary, urinary tract, brain, sebaceous neoplasms
PALB2 [20]	Not described	Breast
STK11 [21] (Peutz-Jeghers syndrome)	Up to 132-fold	Breast, colon, upper GI, lung, reproductive tract
TP53 [22] (Li-Fraumeni syndrome)	Not described	Breast, brain, sarcoma, adrenocortical
PRSS1 [23] (hereditary pancreatitis)	59-fold	None

for the latter should be raised if a patient has a personal or family history of cancer that suggests a hereditary predisposition. A family history of PC is one factor that suggests the possibility of an underlying genetic susceptibility even if nothing is found through genetic testing. As such, PC surveillance should be considered in some individuals with a family history of PC even if no PV is found to be the cause of the cancer diagnoses.

A family is considered to have Familial Pancreatic Cancer (FPC) if at least two family members who are first-degree relatives of each other are diagnosed with PC. Members of an FPC family who have affected first-degree relatives (FDR) have an increased risk for PC; the magnitude of risk is directly correlated to the number of affected FDRs, ranging from a 4- to 6-fold risk with one FDR to 17- to 32-fold with three FDRs [31, 32]. Based on this data, surveillance is recommended for individuals from an FPC family who have an affected FDR.

Differentiating between individuals who have a PV in a PC-related gene and those who have a family history of PC that is not related to an identifiable genetic cause may be important when considering surveillance programs. A recent study indicates that individuals who undergo PC surveillance because they have an identified PV are significantly more likely to have PC, high-grade dysplasia, or other worrisome findings identified through imaging than individuals who undergo surveillance based on family history of PC alone [33•].

The specific surveillance guidelines for who should be offered surveillance as made by the International CAPS Consortium [2•], ACG [3••], and ASCO [4•] are outlined in Table 2. The International CAPS Consortium guidelines are the most restrictive, which is probably primarily a reflection of them being the earliest published of this group; it should be noted that new guidelines from this consortium are in the process of being approved for publication and will likely be available in 2020. Screening is restricted to any individual with Peutz-Jeghers syndrome and to individuals with an affected FDR who have PV in *CDKN2A*, *BRCA2*, MMR genes, or *PALB2* or who are from an FPC family. ASCO's guidelines are the least specific, with a recommendation for surveillance in individuals from an FPC family who have an affected FDR and in individuals who have a PV in a PC-related gene and who have a family history of PC; qualifying family history for the latter group is not specified. The ACG guidelines are the most complete and inclusive. They indicate that surveillance is appropriate for any individual with a PV in *CDKN2A* or *STK11*. They also recommend consideration of surveillance for individuals who have PV in *ATM*, *BRCA1*, *BRCA2*, MMR genes, or *PALB2* and an affected FDR or second-degree relative (SDR). Consistent with the International CAPS Consortium and ASCO, they also propose surveillance for individuals from an FPC family who have an affected FDR. ACG is the only organization to comment on surveillance for individuals with hereditary pancreatitis; they recommend that surveillance be considered for any individual with a PV in *PRSS1*. At our center, we use the ACG guidelines to determine which patients should be considered for surveillance.

Of note, none of these guidelines comment on surveillance for individuals with PV in APC or TP53, although risk for PC is thought to be increased. Although the risk for PC has been described as being up to 5-fold higher for individuals with FAP than the general population [13], the data is limited and there is speculation that some of the individuals reported to have PC may in fact have had periampullary cancers, resulting in an overestimate of risk. As such, at

Table 2. Pancreatic cancer surveillance guidelines

	Organization								
	International CAPS Consortium 2012 [2•]			ACG 2015 [3••]			ASCO 2019 [4•]		
Syndrome or gene	Is FH required?	FH specifications	Age to begin	Is FH required?	FH specifications	Age to begin	Is FH required?	FH specifications	Age to begin
HBOC (BRCA1/2)	Yes	≥ 1 FDR (BRCA2 only)	Not specified	Yes	≥ 1 FDR or SDR	50[a]	Yes	Not provided	Not specified
Lynch syndrome	Yes	≥ 1 FDR	Not specified	Yes	≥ 1 FDR or SDR	50[a]	Yes	Not provided	Not specified
Peutz-Jeghers syndrome	No	–	Not specified	No	–	35	Yes	Not provided	Not specified
FAMMM	Yes	≥ 1 FDR	Not specified	No	–	50[a]	Yes	Not provided	Not specified
ATM	Not included		–	Yes	≥ 1 FDR or SDR	50[a]	Yes	Not provided	Not specified
PALB2	Yes	≥ 1 FDR	Not specified	Yes	≥ 1 FDR or SDR	50[a]	Yes	Not provided	Not specified
FPC	Yes	≥ 1 FDR	Not specified	Yes	≥ 1 FDR	50[a]	Yes	≥ 1 FDR	Not specified

FH family history, *FDR* first-degree relative, *SDR* second-degree relative
[a]Or 10 years before the earliest age of diagnosis in the family if before age 60

our center, we recommend PC surveillance for APC PV carriers on a case-by-case basis, considering it when an individual has a FDR who also has the APC PV and a history PC, ideally confirmed through medical record review. The lack of PC-specific surveillance guidelines for TP53 PV carriers stems from a poor understanding of the risk for PC in these individuals and from the fact that current guidelines do recommend whole-body MRI, which allows for imaging of the pancreas.

Pancreatic Cancer Surveillance: When?

The goal of PC surveillance is to detect advanced precursor lesions or early-stage malignancy so that surgical resection can successfully treat disease. As such, surveillance must begin at an early enough age that an individual will be unlikely to have already developed advanced disease. Likewise, surveillance must be performed often enough that interval disease does not progress to an untreatable stage.

The data regarding when to begin surveillance and how often to perform it is scant. A multi-center US study reporting on the identification of pancreatic lesions through surveillance of high-risk individuals found that increasing age was a significant predictor of identifying a pancreatic cyst, mass, or dilated duct and that lesions were significantly more common in individuals over age 50 [34].

A German study published by Bartsch et al. in 2016 attempted to determine an optimum screening protocol for individuals from FPC families undergoing surveillance [35•]. The authors reported that imaging was significantly more likely to detect pancreatic lesions in individuals over the age of 45, that relevant lesions were significantly more likely to be detected in individuals over the age 50, and that no significant lesions were identified in individuals who underwent surgery before the age 50. Based on this data, the authors concluded that it is appropriate to begin surveillance at age 50 for members of FPC families. This study also found no significant difference in diagnostic yield when comparing a surveillance protocol of annual MRI and annual EUS with a surveillance protocol of annual MRI with EUS every 3 years. Additionally, the study found no significant difference in diagnostic yield between screening every 12 months and screening every 24 months or longer. The authors ultimately did not feel that this data was sufficient to make a recommendation regarding surveillance interval.

Returning to established guidelines, the International CAPS Consortium was unable to reach a consensus regarding the age at which to start surveillance or an appropriate surveillance interval [2•]. The ASCO provisional guidelines did not comment on an age at which to begin screening or how often to perform it [4•]. The ACG recommends annual surveillance for all cohorts; they suggest that individuals with *STK11* PV begin surveillance at age 35, whereas they suggest that all other groups begin surveillance at age 50, or 10 years before the earliest age of PC diagnosis if they occur before age 60 [3••]. At our center, we follow the ACG guidelines for determining when surveillance should begin and how often to perform it.

None of the guidelines address when an individual should stop undergoing surveillance. It is our practice to base this decision on an individual's

physiologic rather than chronologic age, so we will continue to perform surveillance exams as long as a patient would be a candidate for pancreatic surgical resection. Anecdotally, we performed surveillance EUS for a high-risk individual at age 78 and detected a PC. This individual is disease-free 8 years following a total pancreatectomy for a 1-cm adenocarcinoma, living independently with a good quality of life.

Pancreatic Cancer Surveillance: How?

Current modalities for PC surveillance are limited. To date, no biomarker with sufficient sensitivity and specificity has been identified for PC. PC biomarker work is an active area of early detection research, and a number of regional, national, and international studies, like CAPS5 [36] and PanFAM-1 [37], are currently recruiting participants. Until a biomarker is proven to be clinically reliable, imaging is the primary tool that clinicians have to rely upon.

CT imaging is generally frowned upon as an option for PC surveillance because it detects fewer lesions and confers radiation exposure [34]. Other options include MRI with MRCP and endoscopic ultrasound (EUS). To a large degree, the choice between these two options is made based on clinician preference. A Dutch study, however, investigated the differences in efficacy between these modalities [38•]. The authors reported that MRI was superior in detecting cystic lesions, but that 2 sub-centimeter solid lesions that were found to be stage I PCs were only detected through EUS. Ultimately, the authors concluded that the two imaging modalities have complementary uses, but that MRI may have limitations in the early detection of solid lesions. Our site had a similar experience, with the aforementioned 1-cm adenocarcinoma only detected by EUS and not visualized by MRI.

In the absence of data clearly illustrating that one method of surveillance is superior, it may be reasonable to consider the question of cost-effectiveness. A recently published study of the cost-effectiveness of PC surveillance in high-risk individuals found that imaging followed by pancreatectomy for high-risk lesions is more cost-effective than not performing surveillance [39]. These authors concluded that MRI is more cost-effective than EUS for individuals with moderately increased risk (5-fold higher than the general population), but that EUS was the more cost-effective imaging tool for individuals with substantially increased risk (20-fold or higher than the general population). They also indicate that surveillance at 3-year intervals is more cost-effective than annual surveillance and that surveillance is not cost-effective in individuals older than age 75.

With respect to established guidelines, the International CAPS consortium [2•], ACG [3••], and ASCO [4•] all indicate that surveillance should be accomplished with endoscopic ultrasound or MRI/MRCP. None of these organizations recommends one of these modalities over the other. Additionally, ACG and ASCO both point out that surveillance is ideally performed in expert centers. ACG adds that surveillance in conjunction with research protocols is preferred, and ASCO adds that a thorough discussion of the risks, benefits, uncertainties, and limitations should be undertaken before the decision to enter a surveillance program is made. In our practice, we follow the approach advocated by ASCO guidelines and initially meet with any patient referred for PC

surveillance in our clinic. Since we feel it is more important to identify a small solid lesion rather than cystic lesions in the pancreas, EUS is our imaging modality of choice. However, if small cystic lesions or subtle abnormalities are identified, we will incorporate MRI imaging as well, usually alternating every 6 months between the two different modalities.

Pancreatic Cancer Surveillance: Outcomes

PC surveillance following the parameters outlined above is a generally well-accepted practice among experts in the field, but it is worthwhile to consider its value with respect to the ability to identify relevant findings, the ability to differentiate between high-risk and low-risk findings, and the ability to improve survival.

Available data suggests that between 2 and 14% of high-risk individuals undergoing PC surveillance go on to have partial or complete pancreatectomy, indicating that surveillance can detect relevant findings [34, 40–42, 43••]. The indications for surgery are variable and include PC, IPMNs with high grade dysplasia, other high-risk precursor lesions, low-risk precursor lesions, and pancreatic neuroendocrine tumors. The available data suggests some difficulty in determining which screen-detected lesions require surgery, as illustrated by a relatively high rate of surgeries for low-risk lesions. For example, a meta-analysis of screening results for high-risk individuals found an overall surgery rate of 6%, with the pooled proportion of unnecessary surgery being 68% and a pooled screening goal achievement rate of 1.4% [41]. A European study of the benefits of surveillance in high-risk individuals reported that 6% of their FPC cohort underwent surgery but that only 2% were found to have a high-risk lesion on surgical pathology [40]. A more recent publication reporting on the surgical outcomes of screen-detected lesions in high-risk individuals indicates that 42% of the surgeries performed resulted in only low-grade precursor lesions being found on surgical pathology [42].

Little data exists that demonstrates a proven survival benefit in individuals undergoing surveillance. Some recent studies, however, do illustrate that high-risk individuals undergoing surveillance are more likely to have resectable disease if they are diagnosed with PC, which translates to improved survival. For example, Vasen et al. reported that 7.3% of their *CDKN2A* PV carriers were diagnosed with PC while undergoing surveillance and that 75% of these individuals had resectable disease; they also indicated that this group of individuals had a 24% 5-year survival rate [40]. Canto et al. found advanced neoplasia in 7% of their cohort of 354 high-risk individuals, including 14 individuals with PC and 10 individuals with high-grade dysplasia. Ten of the individuals with PC had screen-detected cancers, 9 of which were resectable; the 3-year survival of this group was 85%. Four of the individuals with PC developed disease during a period of non-compliance with surveillance recommendations; none of these individuals had resectable disease, and the 3-year survival rate was 25% [43••].

The paucity of data regarding surveillance outcomes is primarily the result of the fact that such a small portion of the general population undergoes PC surveillance for genetic or familial risk. This reality highlights the importance of performing surveillance for these individuals in conjunction with research

protocols. Despite the limitations that exist, we believe that surveillance is a reasonable consideration for individuals who have an increased risk for PC and that it has the potential to offer the hope of early detection to families that have seen the devastating effects of this disease first-hand.

Compliance with Ethical Standards

Conflict of Interest
Beth Dudley and Randall E. Brand declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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The data from this study suggests that either MRI or EUS can be used as a surveillance tool for individuals at increased risk for PC, but that EUS is better at detecting small solid lesions, which has implications for early detection of PC.

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This prospective data illustrates that high-risk individuals who are compliant with PC surveillance recommendations have a higher likelihood of being diagnosed with high-risk precursor lesions or resectable PC. This study also indicates an improved survival for individuals with screen-detected PC.

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