SMART Approach

Pancreatic Cancer Surveillance in Clinical Practice

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1. Overview

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with over 66,000 new cases in the United States in 2024.[1] The dismal 5-year survival rate of 12% is largely due to late-stage diagnosis.[2] However, early detection rates and improved outcomes may be possible by targeted approaches for high-risk individuals (HRI) with certain genetic and family risk factors for pancreatic cancer.[3-7] This article outlines a practical approach to PDAC surveillance in clinical settings, focusing on identifying and monitoring HRI for early PDAC. We synthesize current recommendations for surveillance (Table 1) and detail lifetime PDAC risk by gene, alongside associated cancers in major hereditary syndromes (Table 2), to guide physicians in optimizing early detection and management strategies.

- The general population should not be screened for PDAC due to the low (but rising) incidence rate.
- Certain genetic pathogenic variants including those in ATM, BRCA1/2, CDKN2A, and PALB2 increase the risk of PDAC.
- Syndromes such as Peutz-Jeghers (PJS), hereditary pancreatitis, Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM), and Lynch Syndrome (with a relative affected by pancreatic cancer) increase the risk of PDAC.
- Familial Pancreatic Cancer includes kindreds with two or more cases of PDAC, of which two cases are directly related.
- Surveillance modalities for PDAC include magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS).
- Surveillance should be conducted annually due to the rapid progression of PDAC and importance of identifying a lesion when it is small and confined to the pancreas.

2. Guideline Recommendations

Who should be referred for consideration of genetic testing and/or surveillance?

Individuals should be referred to an expert pancreatic cancer center for evaluation for pancreatic cancer genetic testing and/or surveillance if the individual has 1) a first-degree relative with PDAC 2) two or more relatives on the same side of the family with PDAC, 3) a known pathogenic variant (PV)/likely pathogenic variant (LPV) associated with increased susceptibility for developing PDAC (e.g., carrier of a germline mutation in BRCA2), 4) a known PV/LPV in a family member associated with an increased risk of developing PDAC. The National Comprehensive Cancer Network (NCCN) also suggests consideration of hereditary cancer testing for individuals of Ashkenazi Jewish ancestry without additional risk factors.[7]

All patients at our center with PDAC are offered genetic testing at the time of diagnosis. If the patient does not carry a known genetic mutation, then first-degree relatives do not need to be referred for genetic testing or surveillance (unless they meet additional criteria). Expert centers that can assist in genetic testing or surveillance for pancreatic cancer can be found through the National Pancreatic Foundation Centers of Excellence, Pancreatic Cancer Early Detection (PRECEDE) Consortium, or Cancer of the Pancreas Screening (CAPS) websites.

Who is a Pancreatic Cancer Surveillance Candidate?

1. An individual with a PV/LPV which is known to increase the risk of pancreatic cancer (see Table 2).

2. An individual with a first degree relative with pancreatic cancer whose family meets criteria for Familial Pancreatic Cancer.

Abbreviations used in this paper: PDAC, Pancreatic ductal adenocarcinoma; FAMMM, Familial Atypical Multiple Mole Melanoma Syndrome; PV, pathogenic variant; LPV, likely pathogenic variant; NCCN, National Comprehensive Cancer Network; ASGE, American Society for Gastrointestinal Endoscopy; AGA, American Gastroenterological Association; CAPS, Cancer of the Pancreas Screening; PRECEDE, Pancreatic Cancer Early Detection; PJS, Peutz-Jeghers syndrome; VUS, variant of uncertain significance; ACG, American College of Gastro-enterology; FDR, First-degree relative; LS, Lynch Syndrome; LFS, Li-Fraumeni Syndrome; USPSTF, U.S. Preventive Services Task Force.

Key words: Pancreatic cancer, genetic testing, surveillance, early detection, pathogenic variants, hereditary syndromes

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Table 1. Society Recommendations for PDAC Surveillance.

Organization	Who Should Have Genetic Testing? Individuals with…	Genes with Family History Recommended for Surveillance	Genes with Family History not Required for Surveillance	Surveillance Recommendations for High-Risk Individuals
American College of Gastroenterology (ACG)[3]	1. Two relatives (one FDR) with PDAC 2. Three or more relatives with PDAC 3. History of hereditary pancreatitis	-ATM -BRCA1/2 -MLH1, MSH2, MSH6, PMS2 (LS) -PALB2	-CDKN2A (FAMMM) -PRSS1 and other hereditary pancreatitis-associated genes -STK11/LKB1 (PJS)	1. MRI and/or EUS every 1 year 2. Age 50 years old or 10 years younger than the youngest case in the family 3. Age 35 years old in PJS
American Gastroenterological Association (AGA)[4]	1. Two or more relatives (at least one FDR) with PDAC	-ATM -BRCA1/2 -MLH1, MSH2, MSH6 (LS) -PALB2	-CDKN2A (FAMMM) -PRSS1 and other hereditary pancreatitis-associated genes -STK11/LKB1 (PJS) -TP53 (LFS)	1. MRI and/or EUS every 1 year; MRI and EUS should be used in combination 2. Age 50 years old or 10 years younger than the youngest case in the family 3. Age 40 years old in CKDN2A and hereditary pancreatitis 4. Age 35 years old in PJS 5. Should occur at expert centers
American Society for Gastrointestinal Endoscopy (ASGE)[5]	Most recent guidelines focus on surveillance of those with high-risk and do not provide specific recommendations on who should undergo genetic testing	-ATM -LS	-Autosomal Dominant Hereditary Pancreatitis -BRCA1/2 -FAMMM syndrome -PALB2 -PJS	1. MRI, EUS, or EUS alternating with MRI every 1 year a. EUS preferred for patients at very high risk for pancreatic cancer like PJS and FAMMM or when EUS can be combined with other procedures b. MRI preferred for patients with risk for adverse events from anesthesia or those who value non-invasive testing 2. Age 50 years old or 10 years younger than the youngest family case 3. Age 40 years old or 10 years younger than the youngest family case for FAMMM 4. Age 40 years old for Autosomal-dominant hereditary pancreatitis 5. Age 35 years old or 10 years younger than the youngest family case for PJS
International Cancer of the Pancreas Screening Consortium (CAPS)[6]	Most recent guidelines focus on surveillance of those with high-risk and do not provide specific recommendations on who should undergo genetic testing	-ATM -BRCA1/2 -MLH1, MSH2, MSH6 (LS) -PALB2	-CDKN2A (FAMM) -STK11/LKB1 (PJS)	1. MRI and EUS every 1 year (alternate imaging modalities) plus fasting blood glucose and/or Hgb Alc 2. Age 50 or 55 years old or 10 years younger than the youngest family case for Familial Pancreatic Cancer Kindred 3. Age 45 or 50 or 10 years younger than the youngest affected blood relative for BRCA2, ATM, PALB2, BRCA1, MLH1/MSH2 4. Age 40 years old or 10 years younger than the youngest affected blood relative for CDKN2A and PJS
National Comprehensive Cancer Network (NCCN)[7]	1. A diagnosis of PDAC (personal history of PDAC) 2. FDR with PDAC (if impossible to test the relative with PDAC) 3. Any blood relative with known PV/LPV 4. Ashkenazi Jewish ancestry without additional risk factors (may be considered for testing)	-BRCA1 -MLH1, MSH2, MSH6, PMS2, EPCAM (LS) -TP53 (LFS)	-ATM -BRCA2 -CDKN2A -PRSS1 and other associated genes with a clinical phenotype consistent with hereditary pancreatitis -STK11 (PJS)	1. MRI and/or EUS every 1 year 2. Age 50 years old or 10 years younger than the youngest case in the family 3. Age 40 years old or 10 years younger than the youngest case in the family for CDKN2A 4. Age 30-35 years old or 10 years younger than the youngest case in the family for STK11 5. 20 years after onset of pancreatitis or at age 40 years old (whichever is earlier) for PRSS1 or hereditary pancreatitis genes 6. Should occur at expert centers
U.S. Preventive Services Task Force (USPSTF)[12]	1. Recommends against screening for pancreatic cancer in asymptomatic adults; no specific recommendations on surveillance			

Abbreviations: First-degree relative (FDR), Pancreatic Ductal Adenocarcinoma (PDAC), Pathogenic Variant (PV), Likely Pathogenic Variant (LPV), Peutz-Jeghers Syndrome (PJS), Lynch Syndrome (LS), Familial Atypical Multiple Mole/Melanoma Syndrome (FAMMM), Li-Fraumeni Syndrome (LFS)

Some hereditary syndromes, such as Lynch Syndrome, may require a family history of PDAC in a first or second-degree relative to meet criteria for surveillance (see Table 1). As shown in this Table 1, there is variability amongst the guidelines for the requirement of family history for various hereditary syndromes. It is also important to acknowledge that there is variable penetrance and expressivity for PV associated with pancreatic cancer, and outcomes can vary among individuals with the same PV.[8]

Which surveillance modalities should be used?

Pancreas protocol MRI or EUS is recommended for high-risk individuals. American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggest using EUS for patients with PJS and FAMMM or when EUS can be combined with other procedures, while MRI is recommended for those at risk for adverse events from proceduralization or those who may prefer non-invasive testing. ASGE, American Gastroenterological Association (AGA), and CAPS consortium

Table 2: Risk of Pancreatic Cancer by Gene and Other Associated Cancers

Gene/Syndrome	Pancreatic Cancer Risk* (%)	Other Associated Cancers	Other Associated Cancer Surveillance and Prevention***
APC (Familial Adenomatous Polyposis)	1-5%	Colon Upper GI Tract Thyroid Central Nervous System Intra-abdominal Desmoids Small Bowel Cancer Hepatoblastoma	Annual colonoscopy; consideration of colectomy Upper endoscopy every 3-5 years Ultrasound every 2-5 years Patient education on signs/symptoms Patient education on signs/symptoms Consider video capsule endoscopy/enterography, especially if duodenal polyposis Consider liver palpation, abdominal ultrasound, and measurement of alpha-fetoprotein during the first 5 years of life
ATM (Ataxia Telangiectasia)	1-5%	Breast Ovarian Prostate	Annual breast MRI and/or mammogram Patient education on signs/symptoms Discuss risk and benefits of PSA testing +/- digital rectal exam
BRCA1 (Hereditary breast ovarian cancer syndrome)	2% (3.8%)**	Breast Ovarian Prostate Melanoma	Annual breast MRI and/or mammogram; consideration of mastectomy Consideration of salpingo-oophorectomy Consider (BRCA1) or recommend (BRCA2) PSA testing Annual dermatologic exam and minimize ultraviolet exposure
BRCA2 (Hereditary breast ovarian cancer syndrome)	5-10% (7.4%)**		
CDKN2A (Familial Atypical Multiple Mole Melanoma)	10-30%	Melanoma	Dermatologic evaluation, supplemented with total body photography and dermoscopy, every 6 months
MLH1, MSH2, MSH6, PMS2, EPCAM (Lynch Syndrome)	5-10%	Colon Endometrial Upper GI Tract Ovarian Urothelial Cancers Brain Cancer Skin Manifestations	Varies by gene, but in general: Colonoscopy every 1-2 years Patient education on signs/symptoms & consideration of hysterectomy Upper endoscopy every 2-4 years Consideration of salpingo-oophorectomy Consideration of annual urinalysis Patient education on signs/symptoms Consider dermatologic exam every 1-2 years
PALB2 (Partner and Localizer of BRCA2)	5-10%	Breast Ovarian	Annual breast MRI and/or mammogram; consideration of mastectomy Consideration of salpingo-oophorectomy
STK11 (Peutz-Jeghers Syndrome)	10-30%	Breast Colon Upper GI Tract Lung Cervical, Ovarian, Uterine Testes	Annual mammogram and/or breast MRI Colonoscopy every 2-3 years Upper endoscopy and video capsule endoscopy/enterography every 2-3 years Education on smoking cessation Annual gynecologic exam, pap smear, pelvic ultrasound; consider hysterectomy Annual testicular exam
TP53 (Li-Fraumeni Syndrome)	5%	Breast Brain Sarcoma, Adrenocortical, Bone Melanoma Colon and Gastric Prostate	Annual mammogram and/or breast MRI; consideration of mastectomy Annual neurologic exam and annual brain MRI Annual whole-body MRI Annual dermatologic exam Colonoscopy and upper endoscopy every 2-5 years Annual PSA testing

*Adapted from Stoffel et al.[13] **Sawhney et al.[5] ***Adapted from NCCN guidelines[7,14]

suggest using MRI and EUS in combination, although there is not a clear consensus on alternating imaging modalities.

When should surveillance occur?

Surveillance should occur annually; however, interval testing and follow-up will change if abnormalities are detected. Age to initiate testing varies based on genetic risk factors and family history. For example, patients with PJS are recommended to start surveillance at age 35 or 40, while those with BRCA2 or ATM are suggested to start surveillance at age 50 or 10 years younger than the youngest case of PDAC in the family (see Table 1).

3. How We Manage Genetic Testing and Pancreatic Cancer Surveillance

Referral to expert center and genetic testing

After a patient is referred to our clinic, we evaluate criteria for genetic testing and/or pancreatic cancer surveillance. The patient meets criteria for genetic testing if the individual has a first-degree relative with pancreatic cancer or two or more relatives on the same side of the family with pancreatic cancer. As previously discussed, if the patient's family member with pancreatic cancer underwent genetic testing and does not harbor a PV/LPV, then the patient does not need to be referred for genetic testing (unless the individual meets additional criteria).

For those patients who appear to be candidates for genetic testing, the patient meets with a genetic counselor, who extensively reviews the individual's family history and creates a pedigree. If the individual elects to undergo genetic testing, genetic panel testing is recommended. Our panel testing includes genes listed in Table 2, among others. We recommend panel testing which prioritizes clinical sensitivity while limiting testing of genes of uncertain significance.[9] Expanded panels with genes associated with non-PDAC susceptibility may be ordered based on review of the patient's family cancer history. Outcomes of genetic testing include detection of a PV, LPV, variant of uncertain significance (VUS), and no genetic mutation. If a PV/LPV is identified, this can lead to a cascade of testing for additional family members, as well as referrals for surveillance of other associated cancers (see Table 2).

Performance of Pancreatic Cancer for Surveillance

No patients are scheduled for surveillance studies without meeting with a physician in our Hereditary GI Tumor Clinic to review the risks, benefits and limitations of PDAC surveillance. Patients are counseled regarding standard of care imaging using EUS and/or MRI scan on an annual basis. Patients are encouraged to participate in research registries including our own institutional hereditary registry, CAPS 5 consortium, and PRECEDE consortium. Patients are advised that we do not have data at the present time which demonstrates that less patients die of pancreatic cancer using this surveillance approach. However, we do review with these patients' data demonstrating we are able to identify PDACs at an earlier stage in high-risk individuals undergoing annual surveillance and highlight one study from the CAPS 5 consortium, which we participated in, showing that approximately 75% of the PDACs identified were at stage I disease and contrast that with findings of only 10 to 15% PDACs are stage 1 in the general population.[10]

The premise that family history can enrich surveillance with germline PV/LPV is also supported by evidence from a recent multicenter study.[11] On the other hand, there is recognition that a large subset of patients who have PV/LPV in BRCA1/2, PALB2, ATM do not have a family history of pancreatic cancer, thereby prompting several societies to recommend surveillance in this population, regardless of family history (see Table 1). We counsel our patients that the detection yield will be lower than the aforementioned CAPS 5 study when including patients without a family history. Based on shared decision making, we allow these individuals to decide if they wish to undergo yearly pancreatic cancer surveillance. Since insurance policies vary, we also counsel the patient to confirm out of pocket costs for testing. Age of surveillance is based on the patient's specific genetic and/or family history (see Table 1). We recommend annual surveillance with MRI and/or EUS. In our experience, EUS is superior for detecting smaller lesions, and thus, we prefer EUS for those higher risk individuals, such as patients with FAMMM or PJS.

In summary, an individual in our program is eligible for surveillance if the patient has a PV/LPV known to increase the risk of PDAC or meets criteria for Familial Pancreatic Cancer. The individual makes an informed decision on whether they wish to undergo PDAC surveillance via annual imaging using EUS or MRI.

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NP contributed to conceptualization, original draft writing, review and editing.
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