Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of only 8% and is estimated to be the second leading cause of cancer-related deaths by 2021. Prior convention held that screening for PDAC would not be beneficial; however, a deeper understanding of the carcinogenesis pathway supports a potential window of opportunity among the target population. Screening for PDAC is not a standard practice among the general population because of its low incidence. However, screening may be beneficial for individuals with familial history, chronic diseases with genetic predispositions, or inherited cancer syndromes, such as hereditary breast ovarian cancer syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, familial atypical multiple mole melanoma, Lynch syndrome (hereditary non-polyposis colorectal cancer), ataxia telangiectasia, and Li-Fraumeni syndrome, all of which have been associated with an increased risk of developing PDAC. The screening strategies among these high-risk individuals are targeted to identify precursor lesions and PDAC at an early resectable stage. This review describes the risk factors for pancreatic cancer, especially the genetic risk factors in high-risk individuals and current screening strategies available for PDAC. (Am J Pathol. 2019, 189: e35; https://doi.org/10.1016/j.ajpath.2018.09.013)
Despite its aggressive nature and high degree of lethality, screening for PDAC is not standard practice among the general population because of its low incidence: individual lifetime risk is approximately 1.5% (National Cancer Surveillance Epidemiology and End Results Program, https://seer.cancer.gov/statfacts/html/pancreas.html, last accessed October 10, 2018), and reliable, noninvasive screening tools are absent (population screening tests of such low lifetime risk require high sensitivity and particularly a specificity >99% to avoid large numbers of false positives for each true positive found by the test). Hence, current screening strategies have largely focused on groups of individuals thought to be at increased risk of pancreatic cancer compared with the general population.

Perhaps 90% of pancreatic cancers are sporadic, but in some individuals, it can be attributed to familial aggregation (7%), chronic diseases with genetic predisposition, or high-risk genetic syndromes (3%). Such familial or genetic predisposition confers an elevated lifetime risk, generally at least fivefold relative risk of PDAC, and these individuals are classified as high risk (HRIs).

### Genetic Risk Factors

Although many genetic defects likely remain unknown, several genetic syndromes associated with PDAC have been discovered. Because genetic syndromes can produce a variety of cancer types, individuals with genetic susceptibility may not have a family history specifically of PDAC. The inherited cancer syndromes, such as hereditary breast-ovarian cancer syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, familial atypical multiple mole melanoma, Lynch syndrome (hereditary nonpolyposis colorectal cancer), ataxia telangiectasia, and Li-Fraumeni syndrome, have all been associated with increased risk of developing PDAC (Table 1). However, because of their rarity, they in total account for only a small fraction of PDACs.

#### ABO Blood Group

The ABO blood group is a genetically defined factor that has been observed in more than two dozen studies since the 1960s to be associated with risk of PDAC. In western countries, including the United States, the non-O ABO blood group is associated with approximately 40% increased risk (95% CI, 26%–57%). Because A, B, and AB blood groups in total compose approximately 56% of the population in the United States, the fraction of PDAC associated with non-O blood groups is nearly 20%, comparable to the amount of PDAC attributable to cigarette smoking and double the amount of PDAC attributable to high-risk genetic mutations. The mechanism of how the ABO blood group is involved in the occurrence of PDAC is not known.

#### Familial Pancreatic Cancer

The term familial pancreatic cancer has been defined to apply to families with two or more first-degree relatives with PDAC. The family does not fulfill criteria for other known genetic syndromes.
Familial pancreatic cancer risk stratification is based on the number of individuals with PDAC and their relationships to the proband. An elevated risk ratio of 32-fold was found in individuals with three first-degree relatives (lifetime risk, 40%), and an elevated risk ratio of 6.4-fold was found among individuals with two first-degree relatives (lifetime risk, 8% to 12%). Also, a higher risk of PDAC has been observed among familial pancreatic cancer kindreds with younger-onset PDAC (age, <50 years; standardized incidence ratio = 9.3%).

Hereditary Breast-Ovarian Cancer Syndrome

Hereditary breast-ovarian cancer syndrome involves drastically increased risk of ovarian and breast cancers secondary to germline mutations in the BRCA1, BRCA2, PALB2, and ATM genes involved in DNA repair mechanisms. Increased breast and ovarian cancer risks are also associated with Fanconi anemia, including FANCC and FANCG genes. Germline mutations in these tumor suppressor genes also confer higher risks of pancreatic cancers (Table 1).

Of the above mutations, BRCA2 has been one of the most commonly identified mutations, and its incidence among familial pancreatic cancer has been as high as 17%. Mutations in this gene impart a relative risk of 3.5 to 10 for development of PDAC. Mutations of BRCA2 are more common in individuals of Ashkenazi Jewish ancestry, who carry a single mutation, 6174delIT, at a frequency of 1.3%.

The BRCA1 mutation, although less well identified, confers 2.5 to 3 times the risk of PDAC. Among BRCA-negative individuals, the partner and localizer of the BRCA2 (PALB2) gene is another DNA defect repair gene and also has been linked to the ATM gene. Although robust evidence through population studies is lacking, a sixfold higher risk of pancreatic cancer has been demonstrated among individuals with PALB2 mutations.

Familial Atypical Multiple Mole Melanoma

Familial atypical multiple mole melanoma is caused by rare germline mutations in the tumor suppressor gene P16INK4A (alias CDKN2A or multiple tumor suppressor gene). It has autosomal dominant inheritance with variable penetrance and is associated with multiple atypical nevi and malignant melanoma among individuals with one or more affected first- or second-degree relatives. Besides the risk of melanoma and nonmelanoma skin cancers, a relative risk 46.6 (95% CI, 24.7–76.4) for PDAC has been observed among p16 mutation carriers.

Lynch Syndrome

Lynch syndrome is caused by defects in DNA mismatch-repair genes, including MSH2, MLH1, MSH1, MSH2, PMS2, and EPCAM. Although this syndrome is generally associated with increased risk of colon cancer, a higher predisposition to pancreatic cancer has also been noted, with pancreatic tumors that have classical medullary appearances with lymphocytic infiltrates and microsatellite instability.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome results from rare mutations in the STK11/LKB1 tumor suppressor gene, with autosomal dominant inheritance. It is characterized by mucocutaneous pigmentation in the lips, buccal mucosa, and peri orbital area. The germline defect predisposes to gastric, pancreatic, and small intestinal cancers and non-gastrointestinal malignancies involving the breast, ovary, endometrium, cervix, and testis. The relative risk of PDAC in patients with Peutz-Jeghers syndrome is 132-fold (95% CI, 44–261-fold) compared with the general population and conveys a cumulative lifetime risk as high as 36% through the ages of 15 to 64 years.

Familial Adenomatous Polyposis

Familial adenomatous polyposis results from mutations in the APC gene, a tumor suppressor gene that codes for synthesis of scaffolding proteins for degeneration of β-catenin and also controls cell cycle progression and microtubule stabilization. Along with risk of colon cancers, familial adenomatous polyposis is associated with a 4.5- to 6-fold risk of PDAC.

Ataxia Telangiectasia

Ataxia telangiectasia occurs from defects in DNA repair due to mutation in the ATM gene. It is an autosomal recessive disorder, characterized by progressive neurologic abnormalities along with immune dysfunction and predisposition to lymphoma and leukemia, resulting from hypersensitivity to ionizing radiation. Monoallelic mutation in the ATM gene results in increased risk of breast cancer and doubled risk of PDAC in comparison with the general population.

Hereditary Pancreatitis

Hereditary pancreatitis (HP) is a rare syndrome resulting in persistent pancreatic injury and inflammation from germline mutations in PRSS1, SPINK1, CTRC, and CFTR, genes with autosomal dominant inheritance and incomplete penetrance. HP causes premature trypsin activation (PRSS1 mutation) or abnormal inhibitors (including chymotrypsin C-CTRC mutation or serine peptidase inhibitor—SPINK mutation). These mutations predispose to chronic pancreatitis and PDAC, with a standardized incidence ratio of 53. The CFTR mutation has also been associated with an early age of onset and a 5.3-fold increased risk of PDAC.
High alcohol intake has been associated with an increased risk of PDAC (relative risk, 1.15; 95% CI, 1.06–1.25) in a recent meta-analysis. Although the pooled analysis demonstrated an increased risk of pancreatic cancer with high liquor intake (risk ratio, 1.43; 95% CI, 1.17–1.74), little or no effect was revealed for what authors categorized as low or moderate drinking.

### Diabetes Mellitus

Diabetes mellitus (DM) appears to have a bidirectional association with PDAC. The onset of DM has been shown to precede occurrence of PDAC by a few years and resolve post-resection in many patients. PDAC seems to lead to DM through a paraneoplastic field mechanism, and this has been attributed to induced insulin resistance from pancreatic polypeptide deficiency or to adrenomedullin secreted in exosomes. Over the longer term, type 2 DM is associated with approximately 1.5-fold increased risk of PDAC. This has been attributed to growth stimulation by endogenous hyperinsulinemia. Increased risks attributed to obesity and metabolic syndrome are also thought to arise from elevated insulin levels. PDAC has also been associated with...
pancreatogenous DM, with common predisposing risk factors leading to exocrine insufficiency. The DM-PDAC relationship is an intense area of research interest and has stimulated work to reduce knowledge gaps pertaining to interactions of chronic pancreatitis (CP), DM, and PDAC development. Surveillance strategies among these populations and the effect of DM treatment on PDAC are important questions, but no clear guidelines have been established yet.

Chronic Pancreatitis

CP is an established risk factor for pancreatic cancer. Chronic inflammation is believed to promote premalignant cell survival, autocrine stimulation of a protumorigenic environment, and desmoplasia. In a meta-analysis, progression of CP to PDAC occurred, on average, over one to two decades, and relative risk of PDAC was estimated at 13.3. Although only 5% of CP patients developed PDAC over two decades, the risk appeared to be much higher among patients with a hereditary predisposition. A recent cohort study reported an older age of onset and a substantial smoking history (>60 pack-years) in a high proportion of patients with CP.

Screening and Surveillance for Pancreatic Cancer

In 2011, the International Cancer of the Pancreas Screening (CAPS) Consortium held a conference, comprising multidisciplinary international experts, and formulated recommendations for screening, surveillance, and management of HRIs. The screening for pancreatic cancer is being performed at various centers as a prospective clinical trial (https://clinicaltrials.gov; identifier NCT02000089). Table 2 displays the various groups/cohorts under the CAPS5 study for PDAC screening among HRIs.

Precursor Lesions

Pancreatic cancer progression has been postulated to occur in a stepwise manner, starting from precursor lesions (Figure 1). Screening and surveillance strategies for HRIs are targeted to identify precursor lesions and PDAC at early and potentially resectable stages. The following three types of lesions have been considered precancerous or precursor lesions that can progress to invasive PDAC.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) are uncommon mucin-producing cystic neoplasms, with a reported prevalence of 23% in a database of individuals with resected pancreatic tumors. These lesions are much more likely to be found among middle-aged women; however, 1% to 8% of cases occur in men. MCNs are solitary lesions, mostly occurring in the body and the tail of the pancreas. They lack communications with pancreatic ducts and are morphologically distinct from other pancreatic precursor lesions. MCNs are characterized by ovarian-like stroma and mucin-producing epithelium and are graded on the basis of cellular atypia and architectural distortion. MCNs have distinct demographic profiles and are unlikely to recur after resection. Given their generally young age at discovery, MCNs are managed by surgical resection and have almost 100% 5-year survival afterward.

Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing epithelial neoplasms that originate from the main pancreatic duct, its contributing branches, or possibly mixed origins. Microscopically, IPMN cells have papillary projections and lack ovarian-like stroma, unlike MCNs.
Main duct IPMNs have a higher predisposition for malignant transformation, compared with branch duct IPMNs, as demonstrated in a longitudinal study in which the 5-year actuarial risk of progression to high-grade dysplasia among main duct IPMNs was of 63%, in contrast to 15% in the branch duct IPMNs ($P < 0.001$).48

IPMN lesions are further stratified on the basis of high-risk stigmata or worrisome features (WFs). High-risk stigmata includes cysts accompanying obstructive jaundice, those with enhancing mural nodules >5 mm, or those with a main pancreatic duct size >10 mm in longest dimension.49 WFs include cysts >3 cm, enhancing mural nodules <5 mm, thickened/enhancing cyst walls, main duct size of 5 to 9 mm, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum level of carbohydrate (or cancer) antigen 19-9, or cyst growth rate >5 mm/2 years or >10 mm during follow-up.50,51

Pancreatic Intraepithelial Neoplasms

Pancreatic intraepithelial neoplasms (PanINs) are microscopic flat or papillary lesions, comprising cuboidal or columnar cells that originate from pancreatic ducts.52 They have variable mucin content and cellular or architectural atypia, by which they are graded. These lesions are graded on the basis of atypia, and early lesions have a different immunohistochemical profile in comparison with advanced lesions. PanINs also display variable genetic alterations with progression of the dysplasia. Although they are potential targets of screening and intervention, progress is limited in accurate detection of PanINs in asymptomatic subjects through cross-sectional imaging and endoscopic ultrasound (EUS). PanINs are associated with focal lobular centric atrophy of the pancreatic parenchyma from surrounding fibrosis around mucinous metaplastic acinar cells.53

Age of Initiation and Termination of Screening

Individuals with a lifetime risk of pancreatic cancer of >5% should consider screening for the disease or its precursors. With present technologies, population-level screening in general is unwarranted. However, individuals who know of their high familial, genetic, or epidemiologic risks should consult with health care providers for consideration of the pros and cons of screening, because a much higher risk of screening false positivity than actual detection will ensue for lifetime risks of <15%. Once screening is chosen, the age to start is a critical parameter for both detection of precursor lesions in a timely manner and health costs and psychological stress among HRIs. The average age of diagnosis of PDAC among individuals with familial PDAC is 68.18 years, but genetic anticipation results in earlier age of onset in successive affected generations.50 The CAPS Consortium recommends screening for familial PDAC beginning at the age of 50 years.44 However, most programs have initiated screening at the age of 40 years, or 10 years before the youngest age of onset for PRSS1 mutation carriers with HP,53 and at the age of 30 years among patients with PJ syndrome, given the younger ages of onset in this high-risk subset.

Imaging Modalities for Screening

PDAC lesions can be detected through various imaging modalities. As a staging modality, computed tomography enables accurate assessment of PDAC resectability and visualization of the upper abdomen.55 However, as a surveillance tool, it has low accuracy in detection of small PDAC lesions and carries some risks associated with radiation exposure. Positron emission tomography—computed tomography is another imaging modality that enables the differentiation of a hypermetabolic state of a neoplasm or precursor lesions versus nodularity associated with chronic pancreatitis.56 The cost of positron emission tomography—computed tomography is high, and its sensitivity is not high enough.

Most centers use magnetic resonance imaging (MRI) and EUS in the detection of small asymptomatic pancreatic lesions. MRI has the benefits of no radiation exposure and helps in better characterization of pancreatic cysts. In conjunction with MR cholangiography, MRI achieves a fairly high diagnostic accuracy (84% sensitivity and 97% specificity) for PDAC detection.57 This is significant because many of the early PDAC lesions have associated ductal or cystic changes rather than discrete masses.

Diffusion-weighted imaging represents an advancement in MRI and detects the brownian movements of water molecules. Factors influencing brownian motion and diffusion-weighted imaging include increased cell density, edema, fibrosis, and altered functionality of cellular membranes.58 The pooled sensitivity and specificity of diffusion-weighted imaging for differentiating PDAC lesions from noncancerous masses are 0.91 (95% CI, 0.84–0.95) and 0.86 (95% CI, 0.76–0.93), respectively.59 EUS is another sensitive modality for PDAC screening without radiation exposure, but it has risks associated with patient sedation and interobserver variation can be higher than in other imaging modalities.60 Typical lesions seen in the pancreas in EUS imaging of the pancreas in high-risk individuals include pancreatic cysts and CP-like changes in the parenchyma.

A prospective multicenter-blinded study evaluated the efficacy of MRI and EUS in detection of lesions among HRIs and demonstrated moderate (55%) agreement in clinically relevant lesions. Both the modalities had good agreement in terms of lesion site (100%) and size (Spearman coefficient, 0.83).51

The disagreement between modalities mostly involved detection of cystic lesions by EUS and solid lesions by MRI, thus supporting complementary use of both modalities.
<table>
<thead>
<tr>
<th>Study</th>
<th>HRI distribution</th>
<th>Age, years*</th>
<th>Follow-up time, months*</th>
<th>Interventions/screening tests (confirmation)</th>
<th>Diagnostic yield</th>
<th>Surgery</th>
<th>Pathology diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentnall et al 76</td>
<td>n = 14 FPC kindreds</td>
<td>41 (28–65)</td>
<td>Surgical: 12–30</td>
<td>EUS (CT, ERCP)</td>
<td>EUS: 10/14</td>
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<td>Dysplasia: 7</td>
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<tr>
<td>Rulyak et al 77</td>
<td>n = 35 FPC kindreds</td>
<td>(1–48)</td>
<td>EUS, ERCP</td>
<td></td>
<td></td>
<td>12</td>
<td>Dysplasia: 12</td>
</tr>
<tr>
<td>Kimmey et al 78</td>
<td>n = 46 FPC kindreds</td>
<td>NA</td>
<td>Up to 60</td>
<td>EUS (ERCP)</td>
<td></td>
<td>12</td>
<td>Dysplasia: 12</td>
</tr>
<tr>
<td>Canto et al 79</td>
<td>n = 38 FPC PJS</td>
<td>56</td>
<td>22.4 (11.3–50.5)</td>
<td>EUS (FNA, ERCP, CT)</td>
<td>EUS: 17/78</td>
<td>7</td>
<td>T2N1: 1</td>
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<tr>
<td></td>
<td></td>
<td>52 (32–77)</td>
<td>(3–12)</td>
<td>EUS (FNA, ERCP, CT)</td>
<td></td>
<td>1</td>
<td>Outside institution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>EUS (MRI, CT)</td>
<td>EUS: 10/44 [mass (n = 3), cystic (n = 7)]</td>
<td></td>
<td>3</td>
<td>PanIN1-2/IPMN: 4</td>
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<tr>
<td></td>
<td></td>
<td>60 (35–85)</td>
<td>44 (5–93)</td>
<td>EUS, MRI (EUS-FNA)</td>
<td>EUS: 25/44</td>
<td>7</td>
<td>SCA: 2</td>
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<tr>
<td></td>
<td></td>
<td>52 (29–77)</td>
<td>Initial screening</td>
<td>EUS, MRI (FNA, ERCP)</td>
<td>EUS: 20/31</td>
<td>5</td>
<td>None: 1</td>
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<tr>
<td></td>
<td></td>
<td>54 (33–86)</td>
<td>Initial screening</td>
<td>MRI, CT (EUS, FNA)</td>
<td>MRI: 16/98</td>
<td>6</td>
<td>PanIN3: 1</td>
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<tr>
<td></td>
<td></td>
<td>63 (31–91)</td>
<td>44</td>
<td>MRI/EUS</td>
<td>MRI/EUS: 26/72</td>
<td>10</td>
<td>PDAC: 1</td>
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<td></td>
<td></td>
<td>56 (39–72)</td>
<td>48 (0–120)</td>
<td>MRI/MRCP</td>
<td>MRI/MRCP: 7</td>
<td>5</td>
<td>PDAC: 5</td>
</tr>
<tr>
<td>Al-Sukhni et al 77</td>
<td>n = 262 FPC: 159 HBOC: 73 p16: 11 PJS: 7 HP: 2</td>
<td>54 (22–89)</td>
<td>50 (0–96)</td>
<td>MRI/MRCP (EUS, MRI, CT, ERCP)</td>
<td>MRI/MRCP: 4</td>
<td>6</td>
<td>PDAC: 3</td>
</tr>
</tbody>
</table>

*(table continues)*
<table>
<thead>
<tr>
<th>Study</th>
<th>HRI distribution</th>
<th>Age, years*</th>
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<th>Interventions/ screening tests (confirmation)</th>
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<th>Surgery</th>
<th>Pathology diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canto et al</td>
<td>n = 216</td>
<td>56.1 (28–79)</td>
<td>28.8 (14–47.2)</td>
<td>EUS, MRI, CT (EUS-FNA)</td>
<td>EUS, MRI, CT, EUS-FNA: 92</td>
<td>5</td>
<td>PNET: 1 MD-IPMN: 1 BD-IPMN-HGD/PanIN3: 2 PanIN1: 1 BD-IPMN-LGD/MDG: 2</td>
</tr>
<tr>
<td>Potjer et al</td>
<td>n = 241</td>
<td>51.28 (20–75)</td>
<td>(0–36)</td>
<td>EUS (FNA)</td>
<td>EUS: 16/30</td>
<td>3</td>
<td>PDAC: 2 IPMN-LGD: 1</td>
</tr>
<tr>
<td>Sud et al</td>
<td>n = 30</td>
<td>49.9 (23–76)</td>
<td>12.9 (0–36)</td>
<td>MRI (EUS)</td>
<td>MRI: 16/40</td>
<td>5</td>
<td>PDAC: 3 BD-IPMN: 1 MT-IPMN: 1</td>
</tr>
<tr>
<td>Del Chiaro et al</td>
<td>n = 40</td>
<td>68.9 (45–93)</td>
<td>24</td>
<td>EUS, CT (MRI, FNA)</td>
<td>MRI: 16/38</td>
<td>1</td>
<td>PDAC: 1 Benign: 1</td>
</tr>
<tr>
<td>Harinck et al</td>
<td>n = 139</td>
<td>51 (20–73)</td>
<td>12</td>
<td>MRI and/or EUS</td>
<td>MRI and/or EUS: 9</td>
<td>2</td>
<td>PDAC: 2</td>
</tr>
</tbody>
</table>
PJS, Peutz-Jeghers syndrome; PNET, pancreatic neuroendocrine tumor; SCA, serous cyst adenoma; WP, Whipple procedure.

Among them, miR-21 has been the most studied, whereas mRNA translation or by facilitation of degradation.64 Other miRNAs, including miR-155, miR-196, and miR-210, are 17- to 25-nucleotide noncoding RNAs that regulate gene expression in both the general population and found both its sensitivity and specificity to be approximately 80% (95% CI, 0.77–0.82).53 As such, carbohydrate (or cancer) antigen 19-9 by itself is inadequate for the detection of precursor lesions or early malignancy among normal individuals or in the general population. In addition, evidence is limited for its utility among HRIs.

Biomarker Screening

The only clinically established biomarker for PDAC is carbohydrate (or cancer) antigen 19-9, a sialylated Lewis blood group antigen expressed by some PDACs but not by normal tissue.62 Carbohydrate (or cancer) antigen 19-9 is used in the monitoring of disease progression and in response to chemotherapy. One study evaluated its accuracy in the general population and found both its sensitivity and specificity to be approximately 80% (95% CI, 0.77–0.82).53 As such, carbohydrate (or cancer) antigen 19-9 by itself is inadequate for the detection of precursor lesions or early malignancy among normal individuals or in the general population. In addition, evidence is limited for its utility among HRIs.

Many novel blood biomarkers have also been examined, including circulating DNA testing for circulating miRNAs or exosomal markers for early PDAC diagnosis. miRNAs are 17- to 25-nucleotide noncoding RNAs that regulate gene function in the post-transcriptional stage by inhibition of mRNA translation or by facilitation of degradation.64 Among them, miR-21 has been the most studied, whereas other miRNAs, including miR-155, miR-196, and miR-210, have been consistently elevated in early PDAC.65 Dysregulated expression of miR-21, miR-155, and miR-196 has also been observed in precursor lesions, like PanIN and IPMN.

Exosomal biomarkers are another class of molecular markers that comprise cell-secreted circulating extracellular microvesicles and their contents enclosed by bilayer membranes. They contain enriched biomaterials of protein, lipid, DNA, and RNA, which can be used as a diagnostic marker. A recent study demonstrated elevated exosomal miR-191, miR-21, and miR-451a among patients with PDACs compared with patients without disease.66 Moreover, circulating exosome-derived DNAs have been analyzed to demonstrate higher frequency of mutant KRAS in PDAC patients than among healthy individuals, although how far in advance of PDAC diagnosis such mutant KRAS could be detected remains unknown.67 Another recent study combined cell-free DNA mutations and circulating proteins for the detection of early pancreatic cancer.68 The test had sensitivities of 69% to 98% and a specificity of >99% in PDAC diagnosis. This test required large blood samples, and its role in pancreatic cancer requires further validation in both the general population and HRIs.

Pancreatic Juice and Pancreatic Cyst Biomarkers

Given a high index of suspicion, precursor lesions not identified via imaging may be detected by analysis of pancreatic juice (aspirate from duodenum) or cyst fluid (obtained from pancreatic cysts). These fluids are rich in protein and DNA released from pancreatic neoplastic or precursor cells.69 These specimens, along with tissue samples from solid lesions, can be analyzed for genetic alterations, including KRAS mutations, gene mutations in pancreatic cysts, and loss of heterozygosity at CDKN2A, RNF43, SMAD4, TP53, and VHL. EUS—fine-needle aspiration accesses cyst wall and cyst fluid samples that can be sent for a range of studies, including molecular testing. The accuracy of these studies for identifying PDAC precursor lesions is uncertain, including in high-risk screening populations.

Analyzing pancreatic juice collected from the duodenum is another approach for screening otherwise asymptomatic patients considered to be at high risk of developing pancreatic cancer. Studies by Kanda et al70 collected secretin-stimulated pancreatic juice specimens and found GNAS mutations in 66% of IPMNs, which was concordant with fine-needle aspiration results. Higher TP53 mutation

<table>
<thead>
<tr>
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<th>Surgery</th>
<th>Pathology diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konings et al93</td>
<td>n = 186</td>
<td>52 (19–75)</td>
<td>44 (0–120)</td>
<td>MRI and/or EUS</td>
<td>MRI and/or EUS</td>
<td>3</td>
<td>PDAC: 2</td>
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<tr>
<td></td>
<td>FPC: 98</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>PanIN2: 1</td>
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<tr>
<td></td>
<td>p16: 53</td>
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<td></td>
<td></td>
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<td>MT-IPMN + MGD: 1</td>
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<tr>
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<tr>
<td></td>
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<tr>
<td></td>
<td>p53: 4</td>
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</table>

*Expressed as mean (range).
†Central tendency is median, not mean.
‡The 5-year survival rate is 24%.

BD, branch duct; CP, chronic pancreatitis; CT, computed tomography; DP, distal pancreatectomy; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; FPC, familial pancreatic cancer; HBOC, hereditary breast-ovarian cancer; HGD, high-grade dysplasia; HP, hereditary pancreatitis; HRI, high-risk individual; IPMN, intrapapillary mucinous neoplasm; LGD, low-grade dysplasia; M1, metastatic cancer; MD, main duct; MGD, moderate-grade dysplasia; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MT, mixed duct; NA, not applicable; p16, p16/CDKN2A mutation; p53, individuals with p53 mutation; PanIN, pancreatic intraepithelial neoplasm; PDA, pancreatic adenocarcinoma; PJS, Peutz-Jeghers syndrome; PNET, pancreatic neuroendocrine tumor; SCA, serous cystadenoma; WP, Whipple procedure.
frequencies were found in advanced lesions, including PanIN-3s and IPMNs with high-grade dysplasia.

Management of Detected Pancreatic Lesions

As with many medical procedures in which experience improves outcomes, screening and subsequent management should, if possible, be obtained at high-volume centers with multidisciplinary teams. Lesions detected on imaging can undergo either observation or curative-intent resection. At present, most lesions in asymptomatic HRIs are not resected but kept under observation. For asymptomatic lesions among HRIs, the consensus is against total prophylactic pancreatectomy. The management of indeterminate solid lesions detected by EUS or magnetic resonance cholangiopancreatography through pancreatic protocol computed tomography scans. Lesions >1 cm or detected on multimodalities may be considered for resection, but definite tissue diagnosis through biopsy is also recommended. The management of indeterminate solid lesions is not clear.

Surgery

Solid Lesions

Although the empirical evidence is weak, it is recommended to confirm solid lesions detected by EUS or magnetic resonance cholangiopancreatography through pancreatic protocol computed tomography scans. Lesions ≥1 cm or detected on multimodalities may be considered for resection, but definite tissue diagnosis through biopsy is also recommended. The management of indeterminate solid lesions is not clear.

Cyst Lesions

Cystic lesions, including MCN and IPMN, are classified on the basis of consensus guidelines, which have been recently updated. Symptomatic cysts (associated with pain, pancreatitis, or jaundice) and those with high-risk stigmata (cysts with obstructive jaundice, enhancing mural nodules >5 mm, or in the main pancreatic duct >10 mm) should be considered for surgery. On the other hand, cysts with WFs are observed by EUS and fine-needle aspiration. In lesions with WFs, main duct involvement, high-grade dysplasia, or confirmation of a mural nodule ≥5 mm favors surgical resection. A recent systematic review included low-risk and non—low-risk (WF and high-risk stigmata) patients to find 10-year progression risks of low-risk IPMNs and higher-risk IPMNs to be 8% and 25%, respectively. These studies were based on general populations, but data to guide a threshold for resection among HRIs are lacking. If selected, surgical resection must be performed at high-volume centers with lower operative mortality and morbidity. The choice of surgery for lesions in HRIs is not completely clear. Although total pancreatectomy yields no risk of recurrence, it can result in brittle diabetes and exocrine insufficiency and necessitates lifestyle changes. Perioperative outcomes of total pancreatectomy versus partial pancreatectomy are variable. Also, curative resection aims to attain gross as well as microscopically negative margins. Although survival seems not to be influenced by PanIN (even high grade) at the margins, it is decreased by residual invasive cancer. In this setting, intraoperative frozen section finds utility, although accompanied with challenges of grading the PanINs.

Outcomes of Screening Programs

The CAPS Consortium defines successful screening by the detection and treatment of high-grade lesions, including PanIN-3, IPMNs, MCNs with high-grade dysplasia, and early resectable T1N0M0 margin-negative pancreatic cancer. Patient information, screening modalities, and outcome measures of various screening studies are shown (Table 3).

Survival Benefit

It is imperative to determine whether a survival benefit exists for patients undergoing pancreatic cancer screening. A systematic review evaluated the benefits of screening programs among HRIs and revealed higher rates of curative resection (60% versus 25%; P = 0.011) and prolonged survival (14.5 versus 4 months; P < 0.001). However, no significant differences in outcomes were seen in patients with IPMNs undergoing surgery. Whether increased survival merely reflects diagnosis earlier in the disease process or represents a truly extended lifespan is currently not established.

Psychological Stress

Psychological stressors associated with screening include perceived mortality risk, cancer-related anxiety, procedural discomfort, and emotional distress, especially for screened individuals, who turn out to have false-positive results. Higher perceived risk has been observed among familial pancreatic cancer family members compared with BRCA2 mutation carriers. Interestingly, some studies have shown that perceived risk, cancer-related worries, intrusive thoughts, and anxiety toward the next procedure have a tendency to decline over time. A study by Harinck et al found the level of clinical depression or anxiety in six respondents to be 9%. Procedure-related discomfort was found in 14% and 15% of those undergoing EUS and MRI, respectively. No correlation was observed between cancer-related worries and surveillance outcomes (pancreatectomy
or shortening of surveillance intervals), and a favorable survival benefit/risk ratio (88%) and feasibility were demonstrated. Levels of anxiety and depression are not well defined for false-positive testing individuals.

Limitations of Screening

Numerous questions regarding PDAC screening in HRIs remain unanswered. Although current imaging modalities are sensitive for the early detection of cystic lesions, PanIN lesions require better characterization for early diagnosis, because they are not easily visualized through regular imaging. Biomarkers are actively sought, but the required exquisite specificity for general screening has kept them elusive for the moment. The preferred screening modality and interval of follow-up among an initially screened population remain to be established. The target population for PDAC screening is still uncertain. In addition, prediction models for PDAC based on the interaction of modifiable and genetic risk factors are required for further identification of the target population. HRIs comprise only approximately 10% of PDAC patients, and early detection of sporadic pancreatic cancers among individuals with no apparent predispositions has only been recently addressed.

Future Prospects

Early diagnosis of PDAC will require better biomarkers or panels of biomarkers and more robust imaging protocols. These improvements are needed to prevent overdiagnosis of clinically nonsignificant lesions as well as omission of significant precursors or early PDACs. These screening and diagnostic modalities will involve simultaneous exploration, such that they enhance and validate one another. However, it seems unlikely that a biomarker panel with specificity >99.9% for precursor lesions or early cancer, as would be needed for general population screening, will be found in the foreseeable future; such accuracies have only been observed for markers of infectious diseases but not for cancers.

The surveillance programs to date have been limited to only research settings, and their more general applicability is presently uncertain. Much attention in PDAC screening outcomes has concerned survival benefit, but other important considerations include surgical morbidity, postoperative quality of life, and psychological stress. In randomized studies, control subjects may not be feasible; prospective studies will need to use larger study samples and longer lengths of follow-up, and particularly have access to cohorts with stored biosamples taken throughout the duration of follow-up.

Recently, National Institute of Health and Care Excellence guidelines for pancreatic cancer were introduced for PDAC surveillance among HRIs (https://www.nice.org.uk/guidance/ng85/chapter/Recommendations#people-with-inherited-high-risk-of-pancreatic-cancer, last accessed September 29, 2018). These guidelines differ from CAPS guidelines, especially in the management of individuals with HP. With further exploration of diagnostic modalities, better understanding of risk factors, and appraisal of available data, the hope is to fill essential knowledge gaps and find an international consensus on optimal management of these at-risk populations.

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References


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