Identification and Screening of Individuals at Increased Risk for Pancreatic Cancer with Emphasis on Known Environmental and Genetic Factors and Hereditary Syndromes

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Summary
Despite recent diagnostic and therapeutic advances, pancreatic cancer still carries a poor prognosis. Screening high-risk individuals is a relatively new concept with regards to pancreatic cancer but is an area of intense study. Significant effort has been invested in identifying risk factors for pancreatic cancer. Risk factors for pancreatic cancer can be classified into three broad categories: demographic, environmental (host), and hereditary (genetic) predisposition. This manuscript will review the risk factors and genetic syndromes associated with increased risk of developing pancreatic cancer, the role of genetic testing in the evaluation of high-risk patients, the available serologic and imaging tests that can be used to screen these individuals, and will summarize the available literature on attempts at pancreatic cancer screening to date.

Introduction and Epidemiology
Despite recent diagnostic and therapeutic advances, pancreatic adenocarcinoma still carries a poor prognosis. In 2009, there will be an estimated number of 42,470 new cases of pancreatic cancer in the United States, and 35,240 patients will succumb to the disease. Pancreatic cancer will account for the fourth highest total of cancer-related deaths in the U.S., despite being only the tenth most common cause of cancer. Furthermore, the 5-year survival rate is only 5%, the lowest of all malignancies, as estimated between the years 1996-2004 [1]. The majority of patients with pancreatic cancer present with metastatic disease, and only 15-20% are determined to be surgical resectable [2]. Presently, there is no effective screening test for pancreatic cancer.
Surgical resection has been the mainstay of therapy in pancreatic cancer. Historically, this approach has conferred a modest benefit in survival in pancreatic cancer. The median survival of pancreatic cancer has been shown to be 2.5 to 8 months without surgical resection, which improves to 13 to 21 months with surgical resection [2]. The overall 5-year survival rate with surgery remains around 20% [3, 4, 5]. Outcomes are dramatically improved in patients with early stage cancers. The 5-year survival rate improved to 32% for lymph node-negative pancreatic cancers and to 41% for node-negative, margin-negative cancers [4].
Adjuvant and palliative chemotherapy are commonly utilized to prolong survival time and for symptomatic comfort. Recent studies with neoadjuvant chemoradiation have been encouraging with respect to reducing perioperative risk of surgical resection, reducing tumor and lymph node burden, and potentially treating micrometastatic disease [6]. Preoperative gemcitabine-based chemoradiation in stage I and II cancers has demonstrated a median survival time of 34 months and a five-year survival rate of 36% in patients who underwent subsequent pancreaticoduodenectomy [7, 8].

Pathophysiology of Pancreatic Cancer
Similar to other cancerous processes, pancreatic cancer arises from genetic dysregulation that can accumulate over time due to demographic, host, and/or environmental factors. The majority of pancreatic neoplasms (80-90%) are adenocarcinomas that arise from epithelial cells in the pancreatic ducts or develop
from resident stem cells [9]. These precursor lesions or pancreatic intraepithelial neoplasias (PanIN) are flat, non-invasive epithelial neoplasms that are classified into three broad categories: PanIN-1, PanIN-2, and PanIN-3 to reflect the degree of dysplasia [10]. The activation of oncoproteins and the inactivation of tumor suppressor genes play a significant role in the progression of PanIN lesions to invasive adenocarcinoma. The K-ras oncogene is typically the first to be activated and has been found in pancreatic duct lesions with minimal atypia (PanIN-1). These changes are followed by the inactivation of CDKN2A (PanIN-2) and the inactivation of p53, DPC4, and BRCA2 (PanIN-3 and invasive adenocarcinoma) [11]. A subset of adenocarcinomas arise from intraductal papillary mucinous neoplasms (IPMN). These are large, mucin-producing papillary epithelial lesions that usually originate from the main pancreatic duct or major branch ducts. Unlike PanIN precursor lesions, IPMN lesions can be easily detected by conventional imaging modalities (CT, MRI, or EUS) [12]. Features that suggest malignancy include large mural nodules, marked dilation of the main pancreatic duct (greater than 15 mm) or clinical symptoms in the patient such as pain, weight loss, and pancreatitis [13].

Risk Factors

Risk factors for pancreatic cancer can be classified into three broad categories: demographic, environmental (host), and hereditary (genetic) predisposition. The most significant demographic factor is advancing age, as 80% of all pancreatic cancers are diagnosed in the age range of 60-80 years [14]. Other demographic factors associated with increased risk of pancreatic cancer include male gender, Ashkenazi Jewish descent, and African-American descent [15]. Host factors that increase risk of pancreatic cancer include smoking and obesity. Smokers have an increased risk of developing pancreatic cancer (odds ratio (OR) of 1.77) with risk correlated to smoking intensity (OR of 2.13 with more than 50 pack/year) [16]. Overweight individuals have an increased risk of developing pancreatic cancer (OR of 1.67) which increases further in obese individuals (OR of 2.58) [17]. The association between the development of pancreatic cancer and diabetes mellitus is less clear. Overall, there is an increased risk of pancreatic cancer with diabetes (OR of 1.82), but recently-diagnosed diabetes (less than 4 years) has a 50% higher relative risk of the malignancy (OR of 2.1) compared to long-standing diabetes (5 years or more) (OR of 1.5) [18].

The likelihood of a hereditary pancreatic cancer predisposition is increased in families that have had relatives with pancreatic cancer. Their degree of risk is proportional to the number of first-degree relatives affected and/or the total number of relatives affected. Familial adenomatous polyposis, Lynch syndrome (hereditary nonpolyposis colorectal cancer) and hereditary breast/ovarian cancer (BRCA1/BRCA2 gene mutations) have been associated with a moderately increased risk (less than 10-fold) of developing pancreatic cancer. Hereditary pancreatitis, Peutz-Jeghers syndrome, and hereditary melanoma due to CDKN2A gene mutations have been associated with the highest risk for developing pancreatic cancer (more than 10-fold) [15].

Challenges in Screening and Treating Pancreatic Cancer

The main barrier to improving outcomes in patients with pancreatic adenocarcinoma remains developing an effective screening regimen that is clinically useful, cost-effective, and reliable in identifying early stage, asymptomatic lesions of the pancreas. At the time of diagnosis, only 7% of pancreatic cancers are localized, 26% are locally advanced, and the majority (52%) is already widespread [1]. The benefit of identifying early stage cancers was illustrated by one study that demonstrated a 78% 4-year survival with asymptomatic patients with stage I adenocarcinomas; however, these are rarely encountered in clinical practice [19]. An ideal test would be diagnostic for asymptomatic individuals as clinical signs and symptoms of malignancy tend to manifest when patients have achieved a significant tumor burden. Despite the clear need for early detection, no currently available test would be cost-effective for screening the general population. Currently, efforts are focused on screening asymptomatic high-risk populations (more than 10-fold increased risk) that have genetic or host factors that predispose them to develop pancreatic adenocarcinoma.

Familial Pancreatic Cancer

Approximately 8% of patients diagnosed with pancreatic cancer have a first-degree relative with a history of pancreatic cancer [20]. Studies based on family history have indicated that individuals with one, two and three or greater first degree relatives with pancreatic cancer have a 4.6 (95% confidence interval (CI): 0.5-16.4), 6.4 (95% CI: 1.8-16.4) and 32-fold (95% CI: 10.2-74.7) increased risk for pancreatic cancer, respectively [21]. Based on this association, familial pancreatic cancer has been defined as a clinical setting where a family has at least two first-degree relatives affected with pancreatic cancer. The lifetime risk (by 80 years) of pancreatic cancer was also increased when there was an early-onset (age 40 years or less) pancreatic cancer in the family. The lifetime risk in families with one to two first degree relatives including at least one early-onset case was 15.7% and 38.9% in families with three first degree relatives. The lifetime risk in families with one to two first degrees relatives including at least one late-onset case (at age 80 years) (2.9%) was similar to sporadic pancreatic cancer cases (3.3%) [22]. Currently, the genetic etiology of most cases of familial pancreatic cancer remains undetermined. Mutations in
the BRCA2 gene have been identified in 6-11% of familial pancreatic cancer families, making it the most significant genetic cause of familial pancreatic cancer identified to date [23, 24]. In contrast, the BRCA1 gene has not been identified as a major cause of familial pancreatic cancer, even in pancreatic cancer families that report a family history of breast and/or ovarian cancer [25]. Other gene mutations have only been found to account for rare cases of familial pancreatic cancer (PALB2 1% [26], palladin in a single familial pancreatic cancer kindred [27]). The PALB2 gene encodes a protein which interacts with BRCA2, and it was hypothesized that mutations in this gene may confer similar cancer risks. However, PALB2 mutations have only been found to account for approximately 1% of familial pancreatic cancer families. A mutation in the palladin gene was reported in a single, large, very-high-risk familial pancreatic cancer kindred. Further studies did not show any association between palladin mutations and familial pancreatic cancer and these mutations have been identified in normal controls as well [28, 29, 30].

**Hereditary Pancreatitis**

Hereditary pancreatitis is characterized by recurrent attacks of pancreatitis with typical onset in childhood. These attacks continue through adult life and can lead to long-term exocrine and endocrine failure [31]. Mutations in the PRSS1 gene are inherited autosomally dominantly and account for approximately 80% of cases of hereditary pancreatitis. This mutation is also associated with an increased risk for pancreatic cancer (up to 53-fold) [32]. This risk is correlated with the duration and severity of pancreatitis attacks, with those having early onset of pancreatitis and long-term progression to diabetes being at greatest risk [33]. Smoking may also interact with PRSS1 mutations as smokers tend to develop cancer 20 years prior to nonsmokers [34].

Cystic fibrosis is a disorder that is associated with the inheritance of two mutated CFTR alleles. Although this syndrome typically presents as lung disease, approximately 10% of cases present as acute or chronic pancreatitis [35]. Cystic fibrosis has also been associated with a significantly increased risk for pancreatic cancer (OR 31.5; 95% CI: 4.8-205) [36]. Inheritance of a single CFTR allele may also confer a modestly increased risk for pancreatic cancer (OR 1.40; 95% CI: 1.04-1.89) [37].

Mutations in the SPINK1 and chymotrypsin C enzyme (CTRC) genes may also increase the risk for developing pancreatitis, but the specific relationship between these genes and the disease is not well defined. Inheritance of a SPINK1 mutation may amplify the risk of pancreatitis due to other factors. For example, SPINK1 mutation carriers have an increased risk for alcoholic chronic pancreatitis and co-inheritance with a CFTR mutation is associated with a 500-fold increased risk for pancreatitis [38, 39]. CTRC has been reported to be a rare cause of idiopathic, hereditary and tropical pancreatitis [40].

**Peutz-Jeghers Syndrome**

Peutz-Jeghers syndrome is characterized by mucocutaneous pigmentation and multiple hamartomatous polyps in the gastrointestinal tract, most commonly affecting the small intestine, and to a lesser extent, stomach and large bowel [41]. Peutz Jeghers syndrome is associated with increased risk for developing multiple types of cancers, including gastrointestinal, breast, lung, ovarian and uterine/cervical cancers. In particular, Peutz Jeghers syndrome is associated with a 132-fold increased risk in developing pancreatic cancer and a cumulative lifetime risk of 36% between the ages of 15 and 64 years [42]. Peutz Jeghers syndrome individuals are predisposed to develop IPMN precursor lesions [43], which can often be detected with conventional imaging [12]. Peutz Jeghers syndrome is caused by germline mutations in the STK11/LKB1 gene. Somatic mutations in this gene are found in 4-6% of sporadic pancreatic cancers as well [44].

**Hereditary Breast and Ovarian Cancer Syndrome**

Hereditary breast and ovarian cancer syndrome is a familial syndrome that is characterized by early-onset breast and/or ovarian cancers. This syndrome results from germline mutations in the BRCA1 and BRCA2 genes which are associated with increased lifetime risk for breast (80%) and ovarian (BRCA1 63%, BRCA2 27%) cancers [45, 46]. BRCA2 mutations are associated with a moderate risk (3.5 to 10-fold) of developing pancreatic cancer, whereas BRCA1 mutations are only associated with a 2-fold increase in risk [47]. As described previously, BRCA2 mutations are present in up to 11% of familial pancreatic cancer kindreds [23, 24]. A small proportion of individuals of Ashkenazi Jewish descent (1.53%) carry a founder mutation in BRCA2, 6174delT, which has been reported in many families with pancreatic cancer [48].

**Hereditary Melanoma due to CDKN2A Mutations**

Approximately 10% of melanomas occur in family clusters, and mutations in the CDKN2A gene can be identified in approximately 40% of high-risk families [49, 50]. The Melanoma Genetics Consortium (GenoMEL), an international melanoma genetics consortium, found that 28% of CDKN2A families included a diagnosis of pancreatic cancer. However, sub-analysis of the data by region showed a large degree of variance in pancreatic cancer risk and Australian families with CDKN2A mutations did not have an increased incidence of pancreatic cancer at all [50]. Therefore, the overall risk of developing pancreatic cancer with a CDKN2A mutation is still unclear.

**Other Genetic Syndromes**

Familial adenomatous polyposis is caused by mutations in the APC gene and is characterized by the development of hundreds to thousands of colonic adenomatous polyps by an early age and a significantly increased risk for developing colorectal cancer. This
Table 1. Summary of genetic syndromes associated with pancreatic cancer risk.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Clinical/genetic testing criteria</th>
<th>Associated cancer risk</th>
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</thead>
<tbody>
<tr>
<td>Hereditary breast/ovarian cancer</td>
<td>BRCA1</td>
<td>Autosomal dominant</td>
<td>1) Personal history of breast cancer and one or more of the following:</td>
<td>Breast 80%</td>
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<td>[76]</td>
<td>BRCA2</td>
<td>autosomal dominant</td>
<td>- diagnosed age less than, or equal to, 45 years;</td>
<td>Ovarian 20-60%</td>
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<td>- diagnosed age less than, or equal to, 50 years with 1, or more, close blood</td>
<td>Pancreas 6%</td>
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<td>relative with breast cancer (age less than, or equal to, 50 years) and/or 1, or more,</td>
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<td>close blood relative with ovarian cancer;</td>
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<td>- two breast primaries when the first is diagnosed before age 50 years;</td>
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<td>- diagnosed at any age with 2, or more, close relatives with breast and/or ovarian cancer;</td>
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<td>- close male blood relative with breast cancer;</td>
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<td>- Ashkenazi Jewish ancestry.</td>
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<td>2) Personal history of ovarian cancer.</td>
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<td>3) Personal history of male breast cancer.</td>
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<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
<td>Autosomal dominant</td>
<td>A clinical diagnosis of Peutz Jeghers syndrome is made when an individual has two or more of the following features:</td>
<td>Breast 32-54%</td>
</tr>
<tr>
<td>[77]</td>
<td></td>
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<td>- two or more Peutz Jeghers syndrome-type hamartomatous polyps of the small intestine;</td>
<td>Colorectal 39%</td>
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<td>- mucoceutaneous hyperpigmentation;</td>
<td>Pancreas 11-36%</td>
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<td>- family history of Peutz Jeghers syndrome.</td>
<td>Stomach 29%</td>
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<td>Ovarian 21%</td>
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<td>Small bowel 13%</td>
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<td>Lung 7-17%</td>
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<td>Uterus 9%</td>
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<td>Cervix 10%</td>
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<td>Testes 9%</td>
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<td>Melanoma 78%</td>
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<td>Peritoneal 25%</td>
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<tr>
<td>Hereditary melanoma</td>
<td>CDKN2A</td>
<td>Autosomal dominant</td>
<td>Individuals and families meeting the following criteria should be considered for CDKN2A testing:</td>
<td>Breast 50-80%</td>
</tr>
<tr>
<td>[78]</td>
<td></td>
<td></td>
<td>- three (synchronous or metachronous) primary melanomas in an individual;</td>
<td>Colorectal 20-60%</td>
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<td>- families with at least one invasive melanoma and two or more other diagnoses of</td>
<td>Stomach 11-19%</td>
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<td></td>
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<td>invasive melanoma and/or pancreatic cancer among first or second degree relatives on the same side of the family.</td>
<td>Ovary 9-12%</td>
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<td>Hepatobiliary 2-7%</td>
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<td>Upper urinary tract 4-5%</td>
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<td>Small bowel 1-4%</td>
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<td>Pancreas 3.6%</td>
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<td>Brain/CNS 1-3%</td>
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<td>Sebaceous skin cancer 1%</td>
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<tr>
<td>Lynch syndrome</td>
<td>MSH2</td>
<td>Autosomal dominant</td>
<td>Individuals and families meeting the following criteria should be considered for Lynch syndrome evaluation:</td>
<td>Colon About 100% w/o colectomy</td>
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<td>[77]</td>
<td>MLH1</td>
<td>dominant</td>
<td>- diagnosed with colorectal cancer less than 50 years of age</td>
<td>Duodenal/ 10%</td>
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<td></td>
<td>MSH6</td>
<td></td>
<td>- synchronous or metachronous Lynch-syndrome associated cancers</td>
<td>peripapillary 0.5%</td>
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<tr>
<td></td>
<td>PMS2</td>
<td></td>
<td>- colorectal with histological features of microsatellite instability in a person less than 60 years of age</td>
<td>Stomach 2%</td>
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<td>- colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with Lynch syndrome related cancers regardless of age</td>
<td>Thyroid 1%</td>
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<td>CNS &lt;1%</td>
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<td></td>
<td></td>
<td>Hepatoblastoma 1.6%</td>
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<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>Autosomal dominant</td>
<td>APC testing should be considered for individuals presenting with 20 or more synchronous or metachronous colon polyps.</td>
<td>Colon About 100% w/o colectomy</td>
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<tr>
<td>[77]</td>
<td></td>
<td>(about 25% due to new mutations)</td>
<td>Duodenal/ 10%</td>
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<td>peripapillary 0.5%</td>
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<td>Stomach 2%</td>
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<td>Thyroid 1%</td>
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<td>CNS &lt;1%</td>
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<td></td>
<td></td>
<td>Hepatoblastoma 1.6%</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1</td>
<td>Autosomal dominant</td>
<td>Individuals meeting the following criteria should be considered for PRSS1 testing:</td>
<td>PRSS1 mutation: 80% risk for pancreatitis and 40% risk for pancreatic cancer</td>
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<tr>
<td>[79]</td>
<td></td>
<td>inheritance</td>
<td>- unexplained pancreatitis episodes in childhood;</td>
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<td>- unexplained chronic pancreatitis.</td>
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<td>Genetic testing can also be considered in individuals who have family history of pancreatitis and the following:</td>
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<td>- unexplained recurrent episodes of pancreatitis;</td>
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<td></td>
<td>- unexplained chronic pancreatitis.</td>
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</tbody>
</table>

* Ovarian cancer in this table refers to epithelial ovarian cancers. Fallopian tube and primary peritoneal cancers should also be included in these criteria.

* Presence of tumor infiltrating lymphocytes, Crohn’s-like reaction, mucinous/signet-ring differentiation, or medullary growth pattern. CNS: central nervous system

syndrome is associated with a low (4-fold) risk of developing pancreatic cancer and has a stronger association with other types of cancer such as thyroid, small bowel, and gastric cancers [47].

Lynch syndrome is caused by mutations in any one of four mismatch repair genes MSH2, MLH1, MSH6, or PMS2. The hallmark features of Lynch syndrome are a greatly increased risk for colon and endometrial
cancers. The predisposition to pancreatic cancer in Lynch syndrome is still unclear at this time. A recent study based on patient reported family history only found an 8.6-fold increased risk (95% CI: 4.7-15.7) and an estimated cumulative risk of 1.31% by age 50 years and 3.68% by age 70 years [51].

Genetic Evaluation for Hereditary Pancreatic Cancer

The initial step of evaluating a patient for familial pancreatic cancer risk is to obtain a complete family history that includes the types and ages of cancer diagnoses of at least first (parents, siblings, children) and second (aunts, uncles, grandparents) degree relatives. Ideally, medical records, pathology reports, and death certificates are obtained to confirm diagnoses and to determine if underlying issues such as pancreatitis were present in relatives who developed pancreatic cancer.

Families exhibiting clusters of other cancers such as breast/ovarian cancer or melanoma may be appropriate candidates for genetic testing. A review by Hall et al. of pedigrees from patients referred to a cancer genetics clinic found that a third of families meeting criteria for familial pancreatic cancer also met testing criteria for other hereditary syndromes [52]. Ideally, genetic testing is performed first in a family member presenting with cancer. The benefit of genetic testing is that if a specific mutation can be identified in a proband, the cancer risks can be accurately determined and appropriate testing can be offered to at-risk relatives to identify high-risk individuals that should have increased surveillance for malignancy. Clinical genetic testing is available for all the conditions discussed in Table 1. At this time, genetic testing for CFTR, SPINK1 and CTRC is not routinely recommended for asymptomatic at-risk relatives because the implications for their risk of pancreatic cancer are unclear at this time [32].

Insurance coverage of genetic testing is becoming more common. Myriad Genetic Laboratories (Salt Lake City, UT, USA), a major provider of cancer predisposition genetic testing, reports that, on average, patients only pay 10% of the genetic test costs with insurance covering the majority of the cost [53]. Misuse of genetic information by health insurers has been a hypothetical concern associated with genetic testing. In 2008, the United States enacted the Genetics Information Nondiscrimination Act (GINA; http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00493:) which provided federal protection against the use of genetic information by health insurers and employers. This law prohibits group and individual health insurance plans form using a person’s genetic information in determining eligibility for coverage of in setting premium rates. GINA also prohibits employers from requiring genetic testing as a condition of hiring or from using genetic information to make employment decisions. GINA defines genetic information as the results of a genetic test, the genetic test result of a family member, or a family history of disease. Limitations of GINA are that it does not prevent the use of genetic information by life or disability insurers, it does not require that insurers cover the cost of genetic testing, and it does not apply to members of the military. Law regarding the use of genetic information by insurers or employers varies across countries and the protections provided by GINA are not available in all areas of the world [54].

As mentioned, known genetic syndromes account for only a small portion of familial pancreatic cancer and testing of known genes will not be appropriate for most families. For families without an identified genetic syndrome, tailored risk assessment can still be provided based on empirical data. As mentioned previously, the risk for developing pancreatic cancer increases significantly with the number of first-degree relatives affected [21].

Computer-based models are also available for estimating pancreatic cancer risk. PancPro, which is available as part of the CancerGene software package (http://www4.utswwestern.edu/breasthealth/cogene/) is a risk assessment software tool which can provide an estimate of the lifetime risk for pancreatic cancer for an individual based on family history. This model estimates the likelihood of a hypothetical, highly penetrant gene in the family, and then calculates the probability that an at-risk relative would have inherited that gene based on their degree of relation to an affected family member and age.

CancerGene also provides tools for estimating the risk of BRCA1/BRCA2 mutations and Lynch syndrome-related mismatch repair mutations, as well as the risks for developing breast, ovarian, colon, and endometrial cancer. A limitation of this model is that it does not take into account other exposures, such as smoking, which may also aggregate in families and contribute to pancreatic cancer risk.

There is a growing public awareness regarding the role of family history in disease susceptibility, and clinicians are often on the front lines for addressing questions and concerns about family risk. Collecting family history, providing detailed risk assessments, and genetic testing can be difficult to incorporate into routine clinical practice. Collaborating with local cancer genetics services can be an efficient way to ensure that patients are offered appropriate cancer risk and genetic testing information. Resources for identifying genetic service providers and research opportunities are included in Table 2.

Biomarkers in Screening: Serum-Based Markers

CA 19-9 has been the most frequently studied biomarker in screening for pancreatic cancer with a median sensitivity of 79% (70-90%) and median specificity of 82% (68-91%) [55]. Other serum biomarkers have been studied (CA 242, tissue polypeptide antigen, tissue polypeptide specific antigen, M2-pyruvate kinase, growth differentiation factor 15 (GDF15, alias MIC1), insulin-like growth
factor binding protein-1 (IGFBP-1), Du-Pan, haptoglobin, serum amyloid A, and proteomic analyses), however, none of these have been clinically proven superior to CA 19-9 [56].

CA 19-9 has a number of significant limitations that preclude its routine use as a screening biomarker in asymptomatic individuals. Multiple non-malignant processes, including acute cholangitis or pancreatitis, can lead to elevated CA 19-9 levels [57]. CA 19-9 is frequently elevated in patients with other GI cancers including: cholangiocarcinoma (67%), gastric cancer (41%), colorectal cancer (34%), esophageal cancer (22%) and hepatocellular cancer (49%) [58]. Furthermore, CA 19-9 does not reliably detect early, small pancreatic cancers [58]. Poorly differentiated tumors also produce less CA 19-9 than either moderately-differentiated or well-differentiated tumors [58].

**Biomarkers in Screening: Tissue-Based Markers**

Various tissue-based markers have been studied in attempts to identify effective screening biomarkers in pancreatic cancer. Most of the research has focused on K-ras, the oncogene present in 90% of pancreatic adenocarcinomas [11]. K-ras mutations have been detected in pancreatic juice, blood, and stool in patients with pancreatic cancer. However, K-ras is non-specific, as these mutations can be present in patients with pancreatitis and other malignancies [59, 60, 61]. The p53 tumor suppressor gene, which affects 50-70% of pancreatic cancers and is a regulator of cell apoptosis, was found to be a non-specific marker as well [62].

Mucin encoding genes are overexpressed in high-grade precursor lesions (PanIN-3) and ductal adenocarcinomas [63, 64]. Wang 2007 *et al.* found that the combined measurement of MUC1 plus cytology and MUC5AC plus cytology in EUS-FNA samples from the pancreas provided significantly higher sensitivity (85% versus 65%, 100% versus 65%) and accuracy (89% versus 73%, 91% versus 72%) for detection of pancreatic cancer compared to cytology alone [65]. Micro-RNA expression has been used to distinguish between normal pancreatic tissue and pancreatic cancer in 90-100% of cases [66, 67].

**Screening with Imaging**

No single imaging modality has been identified as a gold standard for screening individuals at high risk for developing pancreatic cancer. Modalities that have been studied include CT, MRI with MRCP, and EUS, each of which has limitations. CT is frequently used to image the pancreas, however, these scans are relatively insensitive for detecting small pancreatic lesions (less than 15 mm) [68]. Furthermore, in prospective screening studies in asymptomatic populations, CT did not detect pancreatic cancers evident in other imaging modalities [69, 70]. Other limitations of CT scans include allergies to contrast dye and concerns regarding radiation exposure in individuals who would require repeated imaging at intervals and may already be predisposed to cancer [12]. MRI and MRCP do not confer significant radiation exposure and appears to be superior to CT in detecting asymptomatic pancreatic lesions, particularly for

<table>
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<th>Resource, website</th>
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<tr>
<td>National Society of Genetic Counselors (NSGC) <a href="http://www.nsgc.org">http://www.nsgc.org</a></td>
<td>Search nationwide for genetic counseling services</td>
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<tr>
<td>GeneTests at National Center for Biotechnology Information (NCBI) <a href="http://www.genetests.org">http://www.genetests.org</a></td>
<td>Provides information on laboratories offering genetic testing and nationwide genetic services</td>
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<tr>
<td>The Melanoma Genetics Consortium (GenoMEL) <a href="http://www.genomel.org">http://www.genomel.org</a></td>
<td>An international melanoma genetics research consortium that provides and information about resources for families with hereditary melanoma and CDKN2A mutations</td>
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<td>Pancreatic Cancer Genetic Epidemiology Consortium (PACGENE) <a href="http://mayoresearch">http://mayoresearch</a> mayo.edu/petersen_lab/epidemiology.cfm (or +1.800.914.7962)</td>
<td>A national registry of high-risk pancreas and gastrointestinal cancer families. Outside referrals accepted.</td>
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<td>PAGENE member sites include: Johns Hopkins - Baltimore, MD, USA: The National Familial Pancreas Tumor Registry (NFPT) <a href="http://www.pathology.jhu.edu/pancreas/nfptr/index.php">http://www.pathology.jhu.edu/pancreas/nfptr/index.php</a></td>
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IPMs (71% vs. 14%, P<0.001) [12]. The limitations of MRI include significant cost and variability in imaging protocols between centers. In addition, patients may tolerate the study poorly if they have claustrophobia and may not be candidates for the exam if they have certain metallic implants [12].

Endoscopic ultrasonography (EUS) combines endoscopy and high-frequency ultrasonography to provide high-resolution imaging without radiation exposure [12]. EUS produces higher-resolution images of the pancreas than CT or MRI and can evaluate focal lesions as small as 2 or 3 mm [71]. EUS was found in preliminary data to detect 49% more neoplastic lesions than CT or MRCP independent of lesion size [12]. EUS also can be performed in conjunction with fine-needle aspiration (FNA) to examine cytology of suspicious pancreatic lesions. EUS-FNA has a sensitivity of 90% and a specificity of 100% [71]. The limitations of EUS-FNA include limited availability when compared to CT or MRI, and the diagnostic yield of the procedure is highly operator dependent. Inter-observer agreement on EUS abnormalities is also not as uniform as that for CT or MRI [72].

**Initial Screening Attempts**

Several studies have been performed to screen asymptomatic high-risk populations for pancreatic cancer.

One of the earliest studies was performed by the University of Washington in which 14 individuals (both symptomatic and asymptomatic) from three familial pancreatic cancer kindreds were screened using EUS, ERCP, and CT. Seven individuals were referred for pancreaticectomy based on ERCP abnormalities. These individuals were found to have varying degrees of dysplasia (low-grade to high-grade) on histopathological examination. No individuals had invasive adenocarcinoma or a pathologically normal pancreas [73].

In a study from Johns Hopkins, 38 asymptomatic high-risk patients (37 with familial pancreatic cancer and 1 with Peutz Jeghers syndrome) were screened by EUS. Abnormal EUS exams were followed by EUS-FNA, CT and ERCP. Six definitive pancreatic lesions were identified (1 invasive ductal adenocarcinoma, 1 IPMN, 2 serous cystadenomas, and 2 non-neoplastic masses) on EUS. A total of 29 individuals had abnormalities on EUS. These six cases, plus one additional case with abnormal cytology (atypical-neoplastic) found on EUS-FNA, were further evaluated via exploratory surgery and resection as appropriate. Overall yield of significant masses was 5.3% (2/38). The single ductal adenocarcinoma was not detected by either the follow-up CT or ERCP evaluations [69].

A second study, also from Johns Hopkins, evaluated 78 total asymptomatic patients (72 familial pancreatic cancer and 6 Peutz Jeghers syndrome) and 149 controls using annual CT and EUS screening. Overall, eight high-risk participants were found to have significant pancreatic masses (6 IPMN, 1 IPMN that progressed to adenocarcinoma, and 1 pancreatic endocrine neoplasm) for a diagnostic yield of 10.3% (8/78) compared to 0.7% (1/138) in controls [70]. Another finding from this study was that high-risk individuals had a significantly increased likelihood compared to controls for exhibiting EUS features of chronic pancreatitis (OR 17.4, P<0.001) [70].

In a study by Poley et al., 44 asymptomatic high-risk patients (21 familial pancreatic cancer, 2 Peutz Jeghers syndrome, 13 CDKN2A, 3 hereditary pancreatitis, 3 BRCA1, 2 BRCA2, and 1 with known p53 mutation) were screened by EUS [74]. Pancreatic adenocarcinoma was identified in 6.8% (3/44) of cases. At the time of publication, the documented cases of pancreatic adenocarcinoma were still living following surgical resection. Additional precursor lesions (IPMN) were identified in an additional 7 cases. The total yield of the study was 22.7% (10/44).

An extensive 5-year study (2002-2007) on screening asymptomatic individuals in familial pancreatic cancer and melanoma pancreatic-cancer-syndrome kindreds who were likely to have CDKN2A mutations for pancreatic cancer in Europe was recently completed. A total of 76 asymptomatic individuals were selected from the National Case Collection Familial Pancreatic Cancer (FaPaCa; Philipps University of Marburg, Marburg, Germany. fapaca@mail.uni-marburg.de). Twenty-eight individuals were found to have abnormalities on EUS (n=25) and/or MRI/MRCP (n=12). These abnormalities included pancreatic or peripancreatic lesions and parenchymal findings consistent with chronic pancreatitis on EUS and hypo-intense masses, micro/macrocystic lesions, and pancreatic duct irregularities on MRI. Seven of these individuals were referred for surgical exploration and with resection occurring in 6 of these cases. Histopathology revealed 1 case of PanIN-2, 1 case of PanIN-1, 1 case of PanIN-1 in conjunction with a gastric IPMN, and 3 cases of serous oligocystic adenomas. The total yield was 7.9% (6/76) [75].

**Current Recommendations**

There is currently a debate in the medical community regarding the utility of pancreatic cancer screening [12]. On one hand, pancreatic cancer has such a dismal prognosis and the lack of treatment options in advanced, metastatic disease suggests an urgent need to detect these malignancies as early as possible: ideally when they are asymptomatic precursor lesions. On the other hand, surgical options for managing potentially premalignant pancreatic lesions are associated with significant risk and there are no data at this time demonstrating improved survival from screening.

The few studies that have been conducted in high-risk populations have found a high rate of pancreatic lesions (5-22%), and this suggests that screening may be potentially beneficial for highly selected patients. Currently, we should focus on identifying individuals who are genetically predisposed for pancreatic cancer through extensive family history taking and
collaboration with cancer genetic counseling services to provide patients accurate risk-assessment and genetic testing. When possible, high-risk patients should be referred to a research study or centers with a multidisciplinary pancreatic team. Patients should be counseled about the potential benefits and limitations of current screening approaches, so they can make informed decisions about whether or not to pursue screening. Patients should also be advised about the signs and symptoms of pancreatic cancer so they will be aware to seek medical care if they develop. Patients should be counseled regarding lifestyle factors such as smoking cessation and maintenance of a healthy body weight to minimize additional pancreatic cancer risk factors.

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