The Early Detection of Pancreatic Cancer: What Will It Take to Diagnose and Treat Curable Pancreatic Neoplasia?

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Abstract

Pancreatic cancer is the deadliest of all solid malignancies. Early detection offers the best hope for a cure, but characteristics of this disease, such as the lack of early clinical symptoms, make the early detection difficult. Recent genetic mapping of the molecular evolution of pancreatic cancer suggests that a large window of opportunity exists for the early detection of pancreatic neoplasia, and developments in cancer genetics offer new, potentially highly specific approaches for screening of curable pancreatic neoplasia. We review the challenges of screening for early pancreatic neoplasia, as well as opportunities presented by incorporating molecular genetics into these efforts. Cancer Res; 74(13); 3381–9. ©2014 AACR.

Introduction

There are as many as a billion neoplastic cells in a cubic centimeter of a cancer (1). Invasive pancreatic cancers, whose average diameter is 4 cm at the time of diagnosis, contain as many as 25 billion cancer cells. This is clearly a large number of cells, though not much larger than the number of neoplastic cells in other tumor types. The problem with pancreatic cancers is that they have usually metastasized by the time they are diagnosed, and once this occurs, it is virtually impossible to cure most patients (2).

As has been nicely demonstrated for colon cancer, the best hope for reducing the cancer-specific mortality of pancreatic cancer lies in early diagnosis and treatment, ideally at a precancerous stage (3). Six issues, however, need to be addressed for the early detection and cure of pancreatic neoplasia to come to fruition. First, the curable lesions that give rise to advanced, noncurable pancreatic cancers have to be characterized. Second, there has to be a reasonable window of opportunity to detect these potentially curable lesions. That is, the progression from localized curable lesions to advanced cancers has to be slow enough that there is a reasonable chance that the localized lesions can be detected clinically. In this paper, we define "localized" as tumors that have not yet metastasized or advanced to the point that they cannot be removed surgically because of their involvement of other tissues, particularly major arteries. Third, a test has to be developed to detect the compendium of curable localized lesions. This is not a trivial problem for lesions arising in an organ that lies deep in the abdomen. Fourth, because treating lesions in the pancreas is not trivial, there has to be a method to distinguish localized lesions with a reasonable chance of progressing to an advanced cancer from lesions with little or no risk of progressing. Fifth, the prevalence of the disease has to be reasonably high in the population to be screened, such that screening tests with achievable sensitivities and specificities will have a high positive predictive value. Sixth, an evidence base has to be developed that demonstrates that screening actually saves lives.

Using the framework of the six issues described above, this article will review recent developments that bring the early detection of pancreatic cancer closer to clinical practice. Equal emphasis will be placed on the opportunities and on the challenges that lie ahead.

Characterize the curable lesions that give rise to metastatic pancreatic cancer

Pancreatic intraepithelial neoplasia. Pathologists have recognized precursor lesions in the pancreas for more than a century (4). S.P.L. Hulst (Boerhaave Laboratory at Leiden), in 1905, described small microscopic lesions in the pancreas that he felt were in between normal and invasive cancer, which he called "zwischenformen." These lesions, which we now call "pancreatic intraepithelial neoplasia (PanIN)," were subsequently shown to be more common in pancreata with an invasive carcinoma than in pancreata without a cancer, to increase with age, and to harbor many of the same genetic alterations as do invasive adenocarcinomas of the pancreas (5). PanINs have been reported in 16% to 45% of pancreata that do not harbor an invasive cancer (6–8).

PanIN lesions are noninvasive epithelial proliferations within the smaller pancreatic ducts (5). They can be flat or papillary,
and are graded histologically as PanIN-1 (low-grade), PanIN-2 (intermediate-grade), or PanIN-3 (high-grade) based on the degree of architectural and cellular atypia present in the lesion (Fig. 1; ref. 5). Paralleling this histologic progression is a genetic progression. The lower grade lesions (PanIN-1 and PanIN-2) often harbor genetic alterations in the KRAS and p16/CDKN2A genes, whereas the higher grade PanIN-3 lesions and invasive adenocarcinomas, in addition to genetic alterations in KRAS and p16/CDKN2A, also often harbor mutations in TP53 and SMAD4 (9–11). Autopsy studies indicate that low-grade PanINs are found in the pancreata of most adults once they reach middle age (6, 8). High-grade PanINs, however, are rarely found, unless there is an associated invasive pancreatic cancer or the patient has a strong family history of pancreatic cancer (6, 8, 12, 13). In total, these observations support the hypothesis that PanIN lesions are precursors to invasive adenocarcinoma and that there is a progression from normal ductal epithelium, to low-grade PanIN, to high-grade PanIN, to localized adenocarcinoma, and to metastatic adenocarcinoma (5).

**Intraductal papillary mucinous neoplasms.** The second major precursor lesion to be identified in the pancreas was the intraductal papillary mucinous neoplasm (IPMN; refs. 5, 14). Pancreatic cysts are very common, being identified in almost 3% of asymptomatic individuals who undergo a computed tomography scan (15), with IPMN accounting for almost 50% of asymptomatic individuals who undergo a computed tomography scan (15), with IPMN accounting for almost 50% of resected pancreatic cysts (16). IPMNs arise in the larger pancreatic ducts and, as the name suggests, they are typically papillary and often produce copious amounts of mucin. IPMNs are, by definition, larger than PanINs. PanINs are usually <0.5 cm, while most IPMNs are ≥1.0 cm (5). IPMNs are more prevalent in the elderly than in the young, and up to a third of IPMNs harbor an associated invasive adenocarcinoma (9). As is observed with PanINs, low-grade IPMNs often harbor KRAS and p16/CDKN2A gene mutations, and high-grade IPMNs harbor further mutations in TP53 and SMAD4 (5). In addition, the GNAS and RNF43 genes are mutated in a major fraction of IPMNs (17, 18). When an adenocarcinoma arises in association with an IPMN, the IPMN and the invasive carcinoma almost always harbor the same genetic alterations, supporting the hypothesis that IPMNs are a precursor to invasive adenocarcinomas (10).

**Mucinous cystic neoplasms.** Mucinous cystic neoplasms (MCN) are large mucin-producing precancerous lesions of the pancreas that almost always arise in the body or tail of the gland and commonly arise in women (14). They are far less common than IPMNs, accounting for only 16% of resected pancreatic cysts in large surgical series (16). In contrast with IPMNs, MCNs do not significantly involve the pancreatic duct system, and, in contrast with IPMNs, MCNs have a distinctive “ovarian-type” stroma (14). Like IPMNs, however, MCNs can progress to adenocarcinoma. The KRAS, p16/CDKN2A, RNF43, TP53, and SMAD4 genes have all been reported to be mutated in MCNs (though GNAS is not, thereby distinguishing IPMNs from MCNs; refs. 14, 18, 19).

**Small invasive cancers.** Although they are rarely encountered outside of screening trials, there have been several reports of long-term survival (“cures”) of patients with surgically resected small, lymph node negative, pancreatic cancers (20–22). For example, Egawa and colleagues reported that patients with surgically resected stage I pancreatic cancer have a median survival of 78 months and a 5-year survival rate of 58% (21). Similarly, Ishikawa and colleagues reported a 5-year survival rate close to 70% for patients with small (<1 cm) pancreatic cancers who were not jaundiced and who did not have a mass-forming lesion on imaging (22).

In summary, three distinct lesions, PanINs, IPMNs, and MCNs, have each been identified as distinct precursors to ductal adenocarcinomas of the pancreas. These precursor lesions, together with some small invasive cancers, are curable.
Demonstrate a sufficient window of opportunity to detect the curable lesions that give rise to metastatic pancreatic cancer

If early screening is to be effective, curable lesions have to be present for a relatively long period of time before they progress to metastatic carcinoma. If these lesions were fleeting, rapidly progressing to metastatic carcinomas, then screening would have to be performed so frequently as to be impractical.

There is strong direct evidence that IPMNs and MCNs are present for years before they progress to invasive cancer. Some patients with IPMNs report that they had symptoms caused by their IPMNs for years, and some even had symptoms for decades, before their tumors were diagnosed, suggesting that their lesions had been present for years (14). In addition, the average age of patients with noninvasive IPMNs is 3 to 5 years younger than the average age of patients with an IPMN with an associated adenocarcinoma, again suggesting that IPMNs are present for years before they progress to invasive cancer (14). Finally, hundreds of patients with an IPMN have been followed clinically with serial imaging and the vast majority IPMNs are relatively stable over months to years, or at most, grow slowly (23–25). Although the numbers are smaller, similar evidence exists for MCNs (14).

Because of their small size, it is much more difficult to directly observe PanIN lesions. The best estimates of the timeline for the progression of PanIN lesions to invasive carcinoma come from the genetic sequencing studies (26). Iacobuzio-Donahue and colleagues sequenced a series of primary invasive pancreatic cancers and multiple matched metastases from the same patients (26). They applied modeling, similar to modeling used by evolutionary biologists, to the patterns of genetic alterations present in multiple lesions from the same patient, and estimated that it takes at least a decade for a cell with an initiating mutation in the pancreas to progress to what they designated as the parental, non-metastatic founder cell (a cell likely present in an advanced PanIN lesion, before the onset of the invasion required to define the lesion as an adenocarcinoma; ref. 26). This study further estimated that it takes at least another 5 years for the neoplastic clone to develop the ability to metastasize (26). Although the timeline for progression calculated is based on several assumptions, it does correspond nicely to the timeline observed for other epithelial neoplasms (27). For example, Jones and colleagues sequenced a series of well-characterized adenomas and invasive carcinomas of the colon and calculated that, for those lesions that progress to invasive cancer, it takes almost 17 years for a microadenoma to progress into an advanced cancer (28).

Clearly, as in other tumor sites, there is a large window of opportunity to detect potentially curable, neoplastic lesions in the pancreas.

Establish a method to detect curable neoplastic lesions

Two broad approaches have been taken to detect curable neoplastic lesions in the pancreas. The first is imaging, particularly with endoscopic ultrasound (EUS). The second involves molecular methods, such as those to detect circulating mutant DNA shed by the neoplastic lesions.

CT, MRI, and EUS have all been used to detect curable lesions in the pancreas. All three imaging modalities have been compared in a prospective study of 225 asymptomatic high-risk individuals by Canto and colleagues (29). EUS detected a pancreatic abnormality in 43% of patients, in contrast with MRI and CT, which identified lesions in 33% and 11%, respectively. Five of the lesions identified on EUS were resected, of which three were IPMNs with high-grade dysplasia. It is clear that cystic precursor lesions can be detected by existing imaging, and that EUS seems to be the most sensitive modality, and that some of these will be curable, high-grade precursor lesions.

Smaller precursor lesions, such as PanINs, are not directly detectable by EUS, but their presence can be inferred indirectly. PanINs produce small areas of fibrosis called “lobulocentric atrophy,” and when multiple PanIN lesions are present, they create multiple areas of fibrosis that can be detected as changes of chronic pancreatitis by EUS (13, 30). Brune and colleagues demonstrated a linear correlation between the number of PanIN lesions present in a pancreas and the EUS score of the severity of chronic pancreatitis (13). The contribution of imaging to the detection of precursor lesions will only increase as the resolution of imaging improves in the coming years.

Two recent advances highlight the enormous potential of molecular-based approaches as tools for the detection of curable lesions in the pancreas. First, whole exome sequencing of well-characterized cyst-forming precursor lesions has defined the genes targeted (mutated) in each of the different precursor lesions in the pancreas (Table 1). Second, new technologies have been developed that can detect rare mutant alleles, even when these mutant alleles are admixed with a 1000-fold more wild-type alleles (17, 18, 31).

Pancreatic secretion (juice) is a natural place to look for mutant genes shed from precursor lesions in the pancreas and can easily be obtained by stimulating pancreatic juice secretion with secretin, and then collecting the juice with an endoscope (Fig. 2). As noted earlier, both IPMNs and PanINs involve the pancreatic duct system, and mutant DNA from both of these lesions is therefore likely to be shed into the pancreatic juice (32, 33). Indeed, Goggins and colleagues have shown that GNAS mutations can be detected in endoscopically obtained pancreatic juice samples in two-thirds of patients with an IPMN (34). Of note, GNAS mutations were also detected in pancreatic juice samples from patients with a clinically normal pancreas who only later developed an IPMN, portending the power of molecular-based tests (34).

Sequencing pancreatic juice requires endoscopy, which reduces the applicability of juice-based approaches. Kinde and colleagues therefore applied a technology that can be used to detect rare mutant alleles, called SafeSeqS, and showed that it is possible to detect KRAS gene mutations in the plasma of 85% of patients with advanced pancreatic cancer (31, 35). Despite this highly sensitive technique, KRAS gene mutations were only detected in 45% of patients with surgically resectable pancreatic cancer highlighting the difficulties of early tumor detection using blood. Small noninvasive precursor lesions are unlikely to shed large quantities of DNA into the blood. We, therefore,
believe it is unlikely that it will be possible to detect mutant DNA in the plasma of patients with noninvasive precursor lesions such as IPMNs, MCNs, or PanINs (36).

Although beyond the scope of this review, it should be noted that a number of other approaches are being developed to detect early pancreatic neoplasia. These include detecting circulating tumor cells, as well as proteins, mucins, and miRNAs shed by the tumors (37, 38).

In sum, curable lesions of the pancreas, both large and small, are detectable with technologies already in clinical practice, including EUS, MRI, and CT. Molecular-based technologies have enormous potential, particularly if they can be applied to biosamples, such as blood or stool, which are obtainable noninvasively. The resolution of imaging and the sensitivity and specificity of molecular-based screening tools are certain to improve in the coming years, and the two technologies may even be combined with molecular-based imaging (37).

**Distinguishing between precursor lesions and benign mimics**

One of the problems in screening for precursor lesions is that harmless benign lesions can mimic these lesions and lead to overtreatment with just over 20% of pancreatic cysts found to be benign following resection (16, 39–41). Although this is not a significant problem for superficial organs such as the skin (freezing or surgically removing a small harmless skin lesion that mimics an in situ squamous carcinoma is not a substantial problem), these mimickers can be a real problem when more deeply seated organs are studied. For example, H.G. Welch and H.J. Passow (The Dartmouth Institute for Health Policy and...
Clinical Practice, The Geisel School of Medicine at Dartmouth, Hanover, NH) analyzed the literature on screening for breast cancer, and concluded that if 1,000 50-year-old American women are screened annually for a decade, 490 to 670 women will have at least one false alarm (recall mammogram), and that 70 to 100 of the women will have a false positive biopsy recommendation (42, 43).

As troublesome as false positive biopsy recommendations are for breast lesions, such recommendations would be a much greater problem for pancreatic lesions (39–41). The pancreas lies deep in the back of the abdomen and lesions in the pancreas are not easily accessed (2). Furthermore, surgical resection is sometimes the only way to diagnose a lesion definitively, and the surgical resection of pancreatic lesions is associated with significant morbidity and a nontrivial risk of mortality. Tools to distinguish harmless lesions in the pancreas, such as serous cystadenomas (SCA), from true precursor lesions, such as IPMNs and MCNs, are needed, as are tools to distinguish low-grade PanINs, MCNs, and IPMNs from high-grade PanINs, MCNs, and IPMNs.

Genetic markers have the potential to distinguish among the various cystic lesions of the pancreas and therefore could help distinguish harmless lesions and precursor lesions. Wu and colleagues sequenced the exomes of the four most common cystic neoplasms of the pancreas [SCA, IPMN, MCN, and solid pseudopapillary neoplasms (SPN)] and found that each of these four tumors was associated with a specific pattern of genetic alterations (Table 1; refs. 17, 18). SCAs are characterized by VHL gene alterations, SPNs by CTNNB1 (β-catenin) gene mutations, IPMNs by KRAS, GNAS, RNF43, TP53, p16/CDKN2A and SMAD4 gene mutations, and MCNs by KRAS, RNF43, TP53, p16/CDKN2A, and SMAD4 gene mutations (17, 18). The mutations present in the neoplastic cells in these cystic neoplasms are shed into the cyst fluid and therefore can be detected in cyst fluid (Fig. 3). For example, in a study that included analyses of both neoplasms and cyst fluid, 96% of 132 IPMNs were found to harbor a mutation in GNAS and/or KRAS, whereas mutations in these genes were not observed in 44 SCAs (18). With these advances, we can easily envision that harmless cysts of the pancreas will be readily distinguishable from true precursor lesions in the near future.

Distinguishing PanIN lesions that are likely to progress from PanIN lesions that are unlikely to progress to invasive cancer is significantly more complex. PanINs, particularly low-grade PanIN lesions, are fairly common in the population, and yet most do not progress to invasive cancer (6, 7, 8, 44). For example, Andea and colleagues reported that 54% of 152 pancreata resected from patients without a pancreatic malignancy harbored at least one PanIN lesion, yet clearly 54% of the population does not develop pancreatic cancer (45). Indeed, Terhune and colleagues, in a "back of the envelope" calculation estimated that less than 1% of PanIN lesions progress to invasive carcinoma (44). Although it is assumed that the higher grade PanIN lesions (PanIN-3) are more likely to progress than lower grade lesions (PanIN-1 and PanIN-2), there is currently no way, other than resection and histologic examination, to determine the grade of a PanIN lesion. The challenge posed by PanIN lesions will only grow as imaging and molecular detection technologies improve.

Figure 3. Fluid from pancreatic cysts can be aspirated at the time of EUS, and the mutations present in the cyst fluid can suggest cyst type. Illustration by Christian Rose, copyright Johns Hopkins University.
Although genetic markers can be used to distinguish harmless cystic lesions (such as SCA) from those that are precursor lesions (IPMNs and MCNs), genetic markers cannot yet be used to determine the grade of a precursor lesion (17, 18).

**Identify populations at risk for pancreatic cancer who will benefit from screening**

The positive predictive value of any test can be greatly improved by increasing the prevalence of the disease being tested for in the population being tested. The prevalence of pancreatic cancer in the general United States population (all ages) is approximately nine per 100,000, and it rises to approximately 68 of 100,000 in individuals above the age of 55 years (2). This low prevalence is problematic for screening. For example, if 100,000 people over the age of 55 years were screened for pancreatic cancer using a test with a specificity of 98% and a sensitivity of 100%, it would generate 1,999 false-positive test results but only 68 true-positive results. A specificity of higher than 99% would be required for a more acceptable positive predictive value. Alternatively, populations whose risk is elevated above the general population could derive benefit from screening methods that were inadequately specific for the general population.

A variety of factors increase the risk of pancreatic cancer, but after age, a family history of pancreatic cancer seems to increase the risk the most (46). For example, Klein and colleagues followed 5,179 individuals from 838 kindreds enrolled in the National Familial Pancreas Tumor Registry (NFPTR, http://pathology.jhu.edu/pc/nfptr/index.php) and found that individuals in families with at least a pair of first-degree relatives diagnosed with pancreatic cancer (designated "familial pancreatic cancer kindreds") are 9-fold more likely to develop pancreatic cancer than is the general population (47). In the study by Klein and colleagues, the risk of pancreatic cancer rose with the number of family members diagnosed with pancreatic cancer, such that individuals with three first-degree relatives with pancreatic cancer had a 32-fold increased risk (47). Thus, individuals with a strong family history of pancreatic cancer represent a well-defined population with a significantly increased risk.

Risk-prediction models aimed at identifying families that carry a high-penetrance pancreatic cancer gene, such as Pancreatic Prostate, have been developed that can be used to calculate the risk of pancreatic cancer based on disease patterns within a specific pedigree (48). For example, the risk of pancreatic cancer is higher for individuals with two first-degree relatives with pancreatic cancer (e.g., a mother and a brother), than it is for individuals with a first-degree and a second-degree relative (e.g., a sister and an aunt; ref. 48). These models can help identify individuals that may have a greatly elevated risk of developing pancreatic cancer. In contrast, risk models that predict the risk of pancreatic cancer using low-penetrance SNPs as well as known pancreatic cancer risk factors (age, diabetes mellitus, heavy alcohol use, body-mass index, and presence or absence of a family history) have not been shown to identify individuals with a substantially elevated risk of pancreatic cancer (49).

Risk can be further refined when the causative genes are known and individuals can now undergo genetic testing to see whether they carry a familial pancreatic cancer susceptibility gene. A number of genes have been identified that, when mutated in the germline, increase the risk of pancreatic cancer (Table 2; refs. 50, 51). These include BRCA2, ATM, PALB2, p16/CDKN2A, STK11/LKB1, BRCA1, PRSS1, and the genes associated with the hereditary nonpolyposis colorectal cancer syndrome. Importantly, as shown in Table 2, pancreatic cancer risk can often be quantified when the gene is known (51).

Individuals with an inherited genetic abnormality that increases their risk of developing pancreatic cancer, as well as individuals without a known predisposing gene mutation but who are predicted to be at increased risk based on their family history, would therefore be a natural first group to benefit from screening.

Another way to increase the prevalence of a disease in a population is to select members of the population that are known to have a preexisting condition that predisposes to the disease. As noted earlier, two of the precursor lesions in the pancreas form cysts, and cysts can be detected by CT and MRI (15, 52). Approximately 70 million CT scans are performed in the United States every year, and 2.6% of the CT scans that include the pancreas will reveal a cystic lesion in the pancreas.

### Table 2. Genes associated with familial pancreatic cancer

<table>
<thead>
<tr>
<th>Individual/gene</th>
<th>% of Families</th>
<th>Relative risk</th>
<th>Risk by age of 70 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history</td>
<td>1</td>
<td>?</td>
<td>0.5%</td>
</tr>
<tr>
<td>ATM</td>
<td>&lt;2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>BRCA1</td>
<td>&lt;1</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>BRCA2</td>
<td>6–12</td>
<td>3.5–10</td>
<td>3.5%</td>
</tr>
<tr>
<td>HNPPCC-associated genes</td>
<td>?</td>
<td>8</td>
<td>3.7%</td>
</tr>
<tr>
<td>p16/CDKN2A</td>
<td>1–3</td>
<td>20–34</td>
<td>10%–17%</td>
</tr>
<tr>
<td>PALB2</td>
<td>3</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PRSS1</td>
<td>&lt;1</td>
<td>50–80</td>
<td>25%–40%</td>
</tr>
<tr>
<td>STK11</td>
<td>&lt;1</td>
<td>132</td>
<td>30%–60%</td>
</tr>
</tbody>
</table>

Abbreviation: HNPPCC, hereditary non-polyposis colorectal cancer.
This fraction is even higher for patients who have MRI exams (52). The prevalence of cysts detectable by either CT or by MRI increases with age, such that cysts can be found in 7% to 12% of individuals over the age of 70 years (15, 52). Some of these cysts will be the precursor lesions IPMNs and MCNs. When applied to individuals with a pancreatic cyst, tests for markers such as circulating tumor DNA will have a significantly higher positive predictive value than when these same tests are applied to the general population (35).

The screening of patients with multiple risk factors, such as elderly individuals with family history and a pancreatic cyst, would lead to even higher positive predictive values for any early screening test.

**Develop an evidence base establishing that screening at-risk individuals is beneficial**

Demonstrating that screening actually saves lives is extremely difficult (53, 54). Screening for colonic neoplasia and cervical cancers are examples of screening that has been shown to save lives, but this was only shown through very large population studies carried out years after such screening had become routine. For example, among 88,902 participants followed over a period of 22 years in the Nurses’ Health Study and the Health Professionals Follow-up Study, colon cancer mortality was reduced after screening sigmoidoscopy (HR = 0.59) and screening colonoscopy (HR = 0.32). In contrast, evidence in support of pancreatic cancer screening is similar to the evidence that was available to justify colorectal cancer screening 20 years ago, that is, studies suggest that screening can detect asymptomatic precursor lesions, but it is only an expectation that removing these precursor lesions will improve outcomes for patients (55). Ongoing collaborative research enabled by a worldwide Cancer of the Pancreas Screening consortium will provide a larger study population base to determine the yield and clinical outcomes of screening high-risk individuals (55–58). Even so, it will take an extremely large study population followed for many years to show that screening for pancreatic neoplasia actually saves lives (29, 55–59).

**Summary and Conclusions**

It has been established that curable precursor lesions do exist in the pancreas, that these lesions are long-lived before they progress to adenocarcinomas, that curable precursor lesions can be detected, and that groups at high-risk of developing the disease can be identified (Fig. 4). Small invasive cancers are also detectable and small pancreatic adenocarcinomas are much more likely to be surgically curable than are larger ones (20–22). Furthermore, as new medical therapies for pancreatic adenocarcinoma are developed, they are likely to be considerably more efficacious against less advanced cancers than against more advanced ones. Thus, screening tests that detect smaller adenocarcinomas may still be useful, as they could increase the chances of success with subsequent therapy.

As technologies advance and the opportunities for the early detection of pancreatic neoplasia grow, it is likely that patients,
guided by their physicians, will have to decide whether or not to be screened on the basis of an imperfect understanding of the risks and benefits of screening. This situation is not unprecedented, as it has previously been applied to all other effective screening methods at their inception, such as those for colorectal, cervical, and breast tumors. Hopefully, the principles outlined in this review, as well as additional data and common sense, will guide the development and implementation of these tests, as these tests are sorely needed.

Disclosure of Potential Conflicts of Interest

A.M. Lennon is a consultant/advisory board member for Boston Scientific. M. A. Diaz has provided expert testimony for Myriad Genetics and is a consultant/advisory board member for Amgen and Anaeropharma. N. Papadopoulos has ownership interest (including patents) in PGDx and PapGene and is a consultant/advisory board member for Symex-Inostics. K.W. Kinzler has ownership interest (including patents) in PGDx and PapGene Inc., is a consultant/advisory board member for Symex-Inostics, and has licensed inventions through Johns Hopkins University. B. Vogelstein has ownership interest (including patents) in PGDx and PapGene Inc., is a consultant/advisory board member for Symex-Inostics, and has licensed inventions through Johns Hopkins University. R.H. Hruban has ownership interest (including patents) in Myriad Genetics. No potential conflicts of interest were disclosed by the other authors.

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