Published in final edited form as:

Pancreas. 2019 ; 48(5): 591–593. doi:10.1097/MPA.0000000000001299.

Is the Early Detection of Pancreatic Cancer Possible? Its Good News, Bad News

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The National Cancer Institute (NCI) Alliance of Pancreatic Cancer Consortia for Biomarkers for Early Detection hosted a think tank style meeting in Bethesda, MD, on December 12, 2018. The group, led by Sudhir Srivastava, PhD, MPH, broadly focused on three questions. Which are the best populations to screen? What are the best screening tests? And what biosamples need to be collected to evaluate candidate biomarkers? The think tank started with a keynote address from this author, entitled “Challenges and opportunities presented by the biology of pancreatic cancer.” That address forms the basis for this invited editorial.

Let us start with the bad news, the challenges facing the early detection of pancreatic cancer. Clinicians have long feared the rapid progression of pancreatic cancer; the disease can advance from seemingly undetectable on imaging to widely metastatic disease in a matter of months.¹ In fact, Yu and colleagues mathematically modeled data from over 13,000 patients in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database and found that patients with stage I disease were, on average, only 1.3 years younger than patients with stage IV disease.¹ These, and other similar, results suggest that pancreatic cancer rapidly progresses clinically from low-stage to high-stage disease, and that the window of opportunity for early detection is therefore small. The reason for this rapid progression of pancreatic cancer is not clear, but recent pathological studies suggest that the propensity of pancreatic cancer to invade veins may contribute to the rapid dissemination of disease to the liver.²⁻⁴ Histologic studies of pancreatic cancer in two-dimensions and studies of cleared pancreatic cancer in three-dimensions have shown that venous invasion is present in the majority of pancreatic cancers.²⁻⁵ Since the veins of the pancreas drain directly into the liver, this venous invasion gives the neoplastic cells a direct and uninterrupted path to spread, in large numbers, to the liver.

The second major challenge facing early detection efforts is that it can be clinically impossible to distinguish high-grade precursor lesions from low-grade lesions.⁶⁻⁹ As a result, screening efforts will almost certainly detect precursor lesions, including low-grade intraductal papillary mucinous neoplasms (IPMNs), some of which will be “over treated.”¹⁰ That is to say, lesions will be detected and treated that never would have progressed to invasive carcinoma. For example, Sharib and colleagues recently reported that the revised

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The author declares no conflict of interest.

2017 International Consensus Guidelines on the management of pancreatic cysts have, by design, a low sensitivity, resulting in “unnecessary pancreatic resections” at their institution.⁶

Although the bad news is disheartening, there is real good news for those working to develop an approach for the early detection of pancreatic cancer as well. First, we understand the precursor lesions that give rise to invasive ductal adenocarcinoma of the pancreas. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are curable precancerous lesions that can be detected with currently available imaging technologies, while pancreatic intraepithelial neoplasia (PanIN) lesions are usually too small to be detected preoperatively.¹¹ Just as the recognition that adenomas of the colon progress to invasive colon cancer has led to the saving of lives through the detection and removal of non-invasive colon polyps, so too will an understanding of these non-invasive pancreatic precursor lesions form the basis for pancreatic screening.¹²

Second, we understand the genetics of pancreatic neoplasia, including the germline changes that predispose to pancreatic cancer, the somatic genetic alterations in the precursor lesions, and the somatic drivers of invasive pancreatic cancer.¹³⁻¹⁹ These germline genetic events can be used to define populations with an increased risk of developing pancreatic cancer, and the somatic events can form the basis for an early detection test and for tests to better classify pancreatic cysts.²⁰⁻²²

Third, we understand the pathophysiology of pancreatic cancer, particularly alterations in gene, microRNA and protein expression, as well as the downstream metabolic changes that occur as pancreatic cancer develops.²³⁻²⁶ These perturbations may also form the basis for early detection tests.

Fourth, we have been able to identify groups of individuals at higher risk, and these high-risk groups will potentially be the first to benefit from early detection tests. As noted earlier, germline changes, such as *BRCA2* mutations, predispose to pancreatic cancer and these can obviously be identified through sequencing. Other well-characterized risk factors include new onset diabetes in the elderly, obesity, chronic pancreatitis and cigarette smoking.²⁷⁻³⁰ One group of note are patients status post a partial pancreatic resection for an IPMN. Up to 10% of these individuals develop invasive pancreatic cancer in the remnant pancreas.^{31,32} They may represent a high-risk group to target for screening.

Fifth, although, as noted earlier, clinical observations suggest a rapid progression of pancreatic neoplasia, molecular studies suggest that molecular progression takes many years, if not more than a decade.^{33,34} For example, Yachida and colleagues have estimated that it takes as long as 18 years to progress from the mutation that initiates the process to a patient’s death from metastatic disease.³⁴ These data suggest that there should be ample opportunity, if the test is designed to detect early molecular alterations, to detect curable pancreatic neoplasia.

Finally, although the numbers are small, several studies have demonstrated that screening can detect asymptomatic precursor lesions in at-risk individuals, and, furthermore, that

patients with asymptomatic invasive pancreatic cancers detected on screening live longer than do patients whose cancers were detected because they were symptomatic.^{9,35-37}

While all of these advances are wonderfully exciting, there is one last hurdle, and this last hurdle has been eloquently articulated by Muir Gray and colleagues.³⁸ In a thought provoking review on breast cancer screening they wrote: “All screening programmes do harm; some do good as well, and, of these, some do more good than harm at reasonable cost.”³⁸ Before moving forward with any early detection test, we need to consider this “math” behind the early detection of pancreatic cancer.³⁹ For example, we might consider screening individuals in the United States over the age of 55 years using a test with 100% sensitivity and 98% specificity. Taking the prevalence of pancreatic cancer in the United States in this age group as approximately 68 per 100,000, we can estimate that such a test would detect all 68 cancers (the test is 100% sensitive), but even with a 98% specificity it would generate 1999 false positive results! Two thousand people would be falsely alarmed for every 68 cancers correctly detected. The cost of the test itself and the cost of the follow-up testing driven by the false positives would be substantial, never mind the anxiety and potential harm of unnecessary procedures.⁴⁰

Clearly, great care should be taken before a general screening test is introduced. With this in mind, Gray and colleagues have provided six “secrets of successful screening.”³⁸ Listed below, these provide a wonderful framework for considering approaches to the early detection of pancreatic cancer.³⁸

1. Use of “total quality” approach from outset.
2. Clear objectives and standards.
3. Single protocols to enable comparison of results.
4. Single datasets with well understood definitions.
5. Complete and good quality data.
6. Availability of a clear reference point, such as a randomized control trial.

It is this author’s hope that the coming years will see new tools developed that can detect pancreatic neoplasia at an early, curable stage, and that these tools will be applied in a thoughtful and responsible way that save lives while minimizing the costs, both from clinical complications and financial, of the screening program. The National Cancer Institute (NCI) Alliance of Pancreatic Cancer Consortia for Biomarkers for Early Detection brings diverse and deep expertise and resources to bear towards this goal.

Acknowledgments

Supported by the National Institutes of Health, GI SPORE grant, P50 CA62924

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