Screening for Pancreatic Ductal Adenocarcinoma: Are We Asking the Impossible?
Katharine E. Caldwell, Alexander P. Conway, and Chet W. Hammill

ABSTRACT

Pancreatic cancer is projected to become the second leading cause of cancer-related death in the United States by 2020. Because of this, significant interest and research funding has been devoted to development of a screening test to identify individuals during a prolonged asymptomatic period; however, to date, no such test has been developed. We evaluated current NIH spending and clinical trials to determine the focus of research on pancreatic cancer screening as compared with other cancer subtypes. Using statistical methodology, we determined the effects of population-based pancreatic cancer screening on overall population morbidity and mortality. Population-based pancreatic cancer screening would result in significant harm to non-diseased individuals, even in cases where a near-perfect test was developed. Despite this mathematical improbability, NIH funding for pancreatic cancer demonstrates bias toward screening test development not seen in other cancer subtypes. Focusing research energy on development of pancreatic screening tests is unlikely to result in overall survival benefits. Efforts to increase the number of patients who are candidates for surgery and improving surgical outcomes would result in greater population benefit.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), commonly referred to simply as pancreas cancer, is the 11th most commonly diagnosed cancer, but is projected to become the second leading cause of cancer-related death in the United States by 2020, with a median survival rate of less than 6 months (1, 2). Due to an extended asymptomatic period, the majority of patients are diagnosed in late stages with locally advanced or metastatic disease, when surgical intervention is not a viable option. Only 8% of individuals diagnosed with pancreas cancer will be alive 5 years after diagnosis and nearly all who survive to or beyond 5 years are those with early-stage, resectable disease (3, 4). Because of the high mortality rate of late-stage pancreas cancer, a great deal of research has focused on the development of screening strategies that could identify patients in earlier stages of the disease. However, such research has been complicated by the fact that, with less than 0.01% of the total population affected (2, 5), a screening test with both high specificity and sensitivity is needed. Despite significant work in this area, no test has shown promise as a candidate for widespread, population-based screening.

Here, we demonstrate the imbalance of funding in pancreatic cancer to focus on screening, and the improbability of the development of a screening test that would meet World Health Organization (WHO) 1968 consensus criteria for acceptability. We conclude that due to low incidence, few identifiable risk factors to guide stratified screening, and the high complication rates of surgery, the only curative option, the successful development of an effective screening test is mathematically implausible.

Materials and Methods

NIH funding evaluation

NIH funding determinations were made by accessing the NIH Research Portfolio Online Reporting Tools (RePORT). Grants underwent preliminary review to ensure focus on the disease of interest. All studies were reviewed and categorized independently by two authors.

Grants whose self-identified goals included development or improvement of a diagnostic screening tool (radiographic, biomarker, or other method) or identification of precursor lesions were categorized as focused on early diagnosis or detection. Grants researching the use of screening to determine treatment efficacy, perform treatment selection, or monitor for recurrence were excluded. Grants whose self-identified goals included improving surgical outcomes, testing or development of surgical techniques or intraoperative technology were categorized as studies of surgical innovation. To account for differences in total spending by cancer subtype, spending is reported as a percentage of total spending by year of funding.

Clinical trial evaluation

Clinical trial categorization was made by accessing clinicaltrials.gov. Initial search terms were broad, including "pancreatic..."
cancer,” “breast cancer,” and “colon cancer” without specified staging or other criteria. Studies conducted outside of the United States were excluded. Clinical trials in all stages and with all funding sources were included. Studies were first reviewed to ensure focus around the disease of interest. All studies were reviewed and categorized independently by two authors.

Clinical trials with self-identified goals of development of early detection tools were categorized as screening trials. Clinical trials focused on detection of recurrence, treatment selection or monitoring, or detection of other cancer-related events were not considered. Clinical trials whose self-identified goals included improving surgical outcomes, testing or development of new surgical techniques or intraoperative technology were categorized as trials of surgical innovation. Studies that utilized nonoperative procedures were not categorized as surgical trials. To account for differences in the total number of trials available, clinical trials were reported as a percentage of total trials for each disease type.

Criteria for an adequate screening test

The WHO set forth its criteria for defining and determining the appropriateness of a screening test in 1968 (6). By this definition, screening tests are intended to sort out healthy-appearing individuals with disease from healthy individuals without disease. The aim of early detection is to identify individuals at stages of the disease that may not cause symptoms, but that can be treated. According to the WHO, for a screening test to be adequate it must demonstrate several major criteria: reliability, yield, cost, availability of follow-up services, acceptability, and validity.

Reliability and yield refer to aspects of the test itself. A reliable test can be repeated under multiple circumstances with the same result. Yield refers to the measure of previously unrecognized disease diagnosed and brought to treatment.

For our consideration of a screening test for pancreatic cancer, we will assume the reliability and yield of our hypothetical tests to be appropriately high. We will also assume the cost of the test is appropriate for broad, population-based screening.

We will focus on the validity and acceptability of a test as the metrics to judge our hypothetical pancreatic cancer screening tests. Acceptability refers to the willingness of the public to undergo a screening. If a painful or invasive test is required for a disease that does not offer significant risk, that test would not be considered acceptable. Likewise, a test that puts healthy individuals at significant risk of complication or death from screening or from a false-positive result would be unacceptable.

For a test to be considered valid, we must have reasonable certainty that a positive test equates to a diseased person and that a negative test equates to a non-diseased person. We can consider validity in terms of the number of patients who receive a diagnosis who actually have the disease (true positives) in comparison with the number of patients who receive a positive test, but do not have disease (false positives), also known as the positive likelihood ratio. The acceptable ratio of true to false positives depends upon our first criteria of acceptability, as we must consider the consequences of screening and the risk to an individual who receives a false-positive diagnosis. If follow-up tests or treatment carries high risks, the positive likelihood ratio must be higher for a test to be considered acceptable.

Results

Breast cancer screening

As demonstration of this, we will consider a widely accepted and adopted screening test: the use of mammography for breast cancer detection. One in 8 women will develop breast cancer during her lifetime, and there are 330,000 new breast cancer diagnoses made every year (7). Only 5% of these are made in women under 40; thus, mammographic screening has been limited to women over this age (8). There are 62,000,000 women in the United States who qualify for mammography screening, and the yearly incidence of breast cancer in this population is 0.5%.

Breast cancer screening occurs in two phases, a more sensitive, rule-out mammographic test, followed by a specific, rule-in confirmatory biopsy. The sensitivity and specificity of mammographic screening can vary by age, but on average are 87% and 89% (9). If all 62 million women eligible for breast cancer screening underwent mammography, this results in 293,771 women correctly identified with breast cancer (true positives) and 36,309 missed diagnoses (false negatives). It also results in 8,017,090 women without breast cancer who have a test indicating they have breast cancer (false positives).

Many of the women with a false-positive mammogram will undergo repeat imaging or more frequent surveillance with little to no adverse effect. The risk of a recommendation for biopsy in a woman with a falsely positive mammogram is 1.8% annually (10, 11). This results in 144,308 biopsies of nonmalignant lesions. Though the adverse event rate varies by biopsy type and patient factors, the overall risk is 1% risk of infection and 9% risk of bleeding (12). The false-positive rate from a breast biopsy is 7% (11), so 10,102 women will have both a false-positive mammogram and biopsy and would undergo unnecessary surgery. In patients who undergo surgery, those who undergo mastectomy have a 5.8% risk of morbidity and 0.24% risk of mortality, while those who undergo lumpectomy have a 2.2% risk of morbidity and no risk of mortality (13). The majority of morbidity in both groups is due to wound infection (13).

Screening of the at-risk population decreases the number of patients who will die from breast cancer by 26,985 patients, while only increasing the operative mortality by 40 patients (Fig. 1A), even assuming all patients opted for the more morbid mastectomy. Additionally, institution of screening does not result in significant morbidity or mortality among healthy individuals, resulting in 24 morbidities and 586 mortalities among individuals without cancer. The overall gain in cancer-related survival is not overshadowed by the increase in morbidity and mortality among individuals without cancer who receive a false-positive diagnosis as the result of screening.
We can now explore if the combination of mammography and biopsy, a widely accepted screening test, meets our criteria for an appropriate test. The screening results in 293,721 true positives and 10,102 false positives; a positive likelihood ratio of 29:1 (Table 1). If we compare the number of deaths averted to those caused by screening, there are 342 possible cures for every 1 screening-related death. Even when we consider the number of deaths averted compared with the number of individuals who would suffer a morbidity as the result of screening, there are 17 deaths prevented per 1 individual harmed.

When considering a screening test, we must also take into account the screening interval. If a woman has a 1.8% chance of unnecessary biopsy from a single mammogram, over the course of a lifetime her cumulative risk can be calculated as

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**Figure 1.**
Outcomes of screening implementation.
Cumulative risk = 1 – (1 – risk of unnecessary biopsy)\textsuperscript{10 years} = 1 – (1 – 0.018)\textsuperscript{30} = 42%.

The 42% cumulative risk of unnecessary biopsy assumes 30 years of annual screening, beginning at 40 years old, and that the risk of unnecessary biopsy from one mammogram is independent of the previous.

When considering the risks associated with screening, it is important to consider the number of discrete incidents that could lead to harmful effects (10, 14). Despite the fact that an individual has a 42% cumulative risk of unnecessary biopsy due to multiple screening events, she still has low risk of screening-related death or morbidity. It is clear that breast cancer screening can be considered both valid and acceptable based on the low risk of screening itself and the low risk of a false-positive diagnosis.

Colon cancer screening

As a second example, let us consider screening for colon cancer (Fig. 1B). In order to compare a similar paradigm to breast cancer screening, we will consider the use of yearly fecal immunochemical test (FIT) with confirmatory colonoscopy. In this example, colonoscopy alone will not be considered due to its ability to function in screening, diagnostic, and treatment capacities. If we consider adults between 50 and 75 for whom colorectal cancer screening is recommended, the number of new colon cancer cases per year is 148,810, representing a 0.19% yearly incidence.

FIT is considered to be 79% sensitive and 95% specific (15). Testing would result in correct diagnosis of 110,119 (true positives) and incorrect diagnosis of 3,918,960 (false positives) individuals. All patients who receive a positive FIT must undergo confirmatory colonoscopy. If all individuals without cancer who received a positive FIT underwent colonoscopy, assuming a 95% specificity, 195,948 individuals without disease would receive an incorrect cancer diagnosis. This equates to a 1:1.7 positive likelihood ratio of true positives to false positives.

We can assume that with screening, 100% of patients would have cancer detected at early stages in which endoscopic resection could be performed. Without screening, patients are assumed to have presented at the stage they would have otherwise presented: 39% present with localized disease (90% 5-year survival), 40% with regional disease (71% 5-year survival), and 21% with metastatic disease (14% 5-year survival; ref. 5). In the best-case scenario, 100% of patients with localized disease will be operative candidates and will undergo coloscopic removal of their stage 0 or 1 lesion. Up to 33% of patients report one minor symptom after colonoscopy; however, the serious adverse event rate is 0.28%, primarily representing hemorrhage, colonic perforation, or cardiopulmonary events and reported mortality is extremely rare at 0.02% (16). In patients with regional disease, 40% of patients will be considered operable and will undergo resection with reported mortality of 1.5% and morbidity of 17% (17). Although we do not address it here, the cumulative risk of screening by FIT and colonoscopy is more significant due to repeated screening events.

Based on this, screening results in a decrease of 26,834 cancer-related deaths. Due to the decreased morbidity of early-stage resections, screening decreases deaths by 238 in patients with cancer, and only results in deaths of 39 individuals without cancer.

Colonoscopy meets our criteria (Table 1). The positive likelihood ratio is 1:1.7. As this colon cancer screening results in more false than true positives, to determine if this represents a reasonable test, we must consider its acceptability.

The ratio of deaths averted to deaths caused by screening is 192:1, and only 39 individuals suffer screening-related death. Even when we consider individuals who could be harmed by screening, due to the minimally invasive nature of colonoscopic intervention, there are 15.2 deaths averted for every individual harmed. Despite the fact that for every individual correctly identified with cancer, 2 individuals are incorrectly identified, individuals are unlikely to be harmed by an incorrect diagnosis.

We can explore if the combination of FIT and follow-up colonoscopy meets our criteria (Table 1). The positive likelihood ratio is 1:1.7. As this colon cancer screening results in more false than true positives, to determine if this represents a reasonable test, we must consider its acceptability.

Table 1. Screening test characteristics.
investigation for cancer from a more invasive procedure (surgical resection) to a less morbid procedure (endoscopic resection). Thus, we conclude that the combination of FIT and colonoscopy testing would meet our criteria for an appropriate screening test.

**Hypothetical pancreatic cancer screening**

As our previous examples demonstrate, when considering population-based screening, it is prudent to recommend screening for prevalent cancers due to the high number of people helped by screening as compared with the number of individuals harmed by false-positive screens. To demonstrate the difficulty of designing a screening test for a low incidence cancer, such as pancreas cancer, we will present both a realistic and a highly optimistic example of hypothetical screening tests.

Our first example (Fig. 1C) addresses a realistic screening of the at-risk U.S. population. It is clear that a screening test for pancreas cancer could not be applied to the entirety of the population without incurring unnecessary cost and harm to individuals with negligible risk. Many screening tests for cancer are limited by age, such as colon and breast cancers; thus, it is reasonable to limit our hypothetical screening test in hopes of improving detection and preventing unnecessary harm.

Recent census data estimate there are 86,000,000 individuals over 55 in the United States. There are 45,000 new pancreatic cancer diagnoses made each year; according to SEER data, 90% of these occur in adults over 55 (5); thus, we will limit screening to this population.

Currently, patients who develop pancreatic cancer undergo no screening. These patients present at various stages of disease: 53% with metastatic disease (3% 5-year survival), 37% with regional disease (12% 5-year survival), and 10% with localized disease (37% 5-year survival; ref. 5). With no screening, of the 40,500 patients with pancreatic cancer, 36,416 will die of their disease within 5 years (Fig. 1C). Assuming the best-case scenario in which 100% of localized disease and 20% of regional disease is amenable to surgery, 3,889 patients will be alive at 5 years. Of those who underwent surgery, 195 will die from surgical causes and another 1,409 will experience operative morbidity.

We can determine the effects of a hypothetical biomarker screening test for pancreas cancer that is 90% sensitive and 90% specific, an accurate representation of other oncologic screening tests currently in use. We assume that patients who received a positive result from biomarker screening would then undergo confirmatory testing with endoscopic ultrasound (EUS)-guided biopsy (18, 19). EUS is the recommended diagnostic modality for patients with suspected pancreas cancer (20) with sensitivity of 90% and specificity of 90% to 100% (21). EUS is not a benign procedure, with a 4% to 14% risk of complication including esophageal perforation (0.06%), bacteremia (0–8%), pancreatitis (0–2%), and hemorrhage (4%; ref. 22).

Assuming this dual testing strategy, 36,450 patients with cancer would be identified (true positives). We will assume the best-case scenario exists and all 36,450 were detected at early stage with localized disease and 100% of them are surgical candidates. The remaining 4,050 false negatives would present with disease in the expected ratios of a non-screened population.

From the first round of screening by our hypothetical biomarker test, 8,595,950 healthy individuals would be incorrectly identified as having pancreas cancer (false positives). Of the 8.6 million individuals with a false positive on initial screening, 429,798 will also have a falsely positive EUS and will be given an incorrect diagnosis of pancreas cancer. Considering the positive likelihood ratio, we find one individual is correctly identified as having pancreas cancer versus 12 healthy individuals incorrectly identified, or a ratio of 1:12 true to false positives (Table 1).

Surgical resection is the only curative option for early-stage pancreatic cancer; therefore, we assume all patients with a positive diagnosis will be considered for operative intervention. Early-stage resection of pancreas cancer can result in a 20% to 30% cure rate (23). Assuming an aggressive cure rate of 30%, this results in the potential cure of 10,388 patients. However, we must also consider the associated risks of unnecessary surgery in individuals without the disease. Mortality of pancreatic resections is known to vary by center; at high-volume centers the 90-day mortality of a pancreaticoduodenectomy is as low as 4%, compared with a population-based mortality of 8% (24–28). Mortality from distal pancreatectomy is significantly lower, at 0.5% (29). In both cases, morbidity after pancreatic resection is significant, ranging from 20% to 50%. Sixty-five percent of pancreatic cancer is located in the head of the pancreas, 15% in the body and tail, and the other 20% is considered diffuse. We can use an optimistic estimate that 35% of all individuals with pancreatic cancer will have sites in the body or tail and will be candidates for the less morbid distal pancreatectomy (30).

Let us assume that all patients identified by screening are candidates for operative resection and undergo resection at a high-volume center, the best-case scenario. Early detection allows us to increase the number of individuals with cancer who are alive at 5 years from 3,889 to 13,500. However, this increase in cancer-related survival is overshadowed by morbidity and mortality among individuals both with and without cancer. Although screening results in 9,611 additional individuals with cancer who reach 5-year survival, 12,764 individuals, the majority of whom did not have cancer, die as the result of screening and 91,982 individuals would suffer surgical morbidity. This equates to a 1:1.3 ratio of deaths averted to deaths caused by screening and a 1:9.6 ratio of deaths averted to major morbidity events caused by screening (Table 1).

Evaluating this 90% sensitive and specific test by our criteria of validity and acceptability, we can conclude that this test is not valid, with more false than true positives identified. We can also conclude that such a screening test is not acceptable, as the risk of death or morbidity caused by screening is greater than the number of individuals cured by early detection.
We will now consider a near-perfect pancreas cancer screening test in our group of individuals over 55 (Fig. 1D). Although most screening tests currently in use have not been able to achieve such high levels of specificity, the UKCTOCS trial was able to demonstrate a specificity as high as 99.8% with 90% sensitivity for ovarian cancer (31). Thus, we will hypothesize that an even more perfect test could be developed, achieving 99.9% specificity and sensitivity.

This would identify 40,459 individuals with pancreas cancer and only miss 41 people; however, there would still be 8,596 healthy individuals who are believed to have cancer after testing. This screening results in an additional 11,636 individuals with cancer surviving to 5 years; however, it also results in 239 deaths and 1,719 morbidities in individuals without cancer (Fig. 1D). Although there are 8.5 deaths averted for every death caused by screening, the number of individuals who suffer morbidity as the result of screening is nearly identical to the number of individuals cured with 1 morbidity per 1.1 cure (Table 1).

Of note, this scenario results in the immediate death of 1,123 patients with early-stage pancreatic cancer. Due to the long asymptomatic window of pancreatic cancer, without screening these patients could be presumed to live several more years.

We must more closely consider if this near-perfect screening test would meet our criteria for an appropriate test. Our positive likelihood ratio is 2:1, so we could consider this screening to be valid. However, this test could not be considered acceptable at the population level as near equal numbers of individuals are harmed as potentially cured due to the poor survival outcomes in early-stage pancreas cancer, and the significant risk of morbidity and mortality from pancreatic cancer surgery. Additionally, this analysis ignores the cumulative lifetime screening risk, which would increase the harm from frequent screening.

High-risk subgroup screening

Significant attention has been paid to the possibility of screening high-risk individuals based on suggestive symptoms, such as the development of diabetes (32). Type-2 diabetes is common in the general population, with 1.5 million new cases diagnosed in the United States each year (33). The relative risk of pancreatic cancer among individuals with new-onset diabetes is double that of the general population (34). With an incidence of 0.02% in this population, 300 individuals within this cohort would be presumed to have pancreatic cancer. Screening newly diagnosed individuals with our 90% sensitive and specific hypothetical test and follow-up EUS screening results in 270 true-positive diagnoses, but also 14,997 false positives, a ratio of 1:55 (Table 1). Carrying this through, we find for every 1 mortality avoided by screening, 6 individuals die due to screening and 42 individuals are harmed. Even with our near-perfect 99.9% specific and sensitive test that would correctly identify nearly all 300 individuals with pancreatic cancer, the number of false positives is still half those correctly identified (Table 1). Although 6 deaths could be averted for every death caused by screening, just over 1 person would be harmed by screening as would be helped. Further, due to the low annual incidence of pancreatic cancer even in this cohort, screening helps less than 100 individuals.

An estimated 1.95 million people are considered to carry a high-risk genotype for pancreatic cancer (such as BRCA2; ref. 4). As familial pancreatic cancer is responsible for 10% of all cases (4,500 cases/year), we can calculate a yearly incidence of 0.2% in this cohort, 20 times higher than that of the general population. If these 1.95 million individuals underwent screening with a 90% specific and sensitive test, of the 4,500 new cases, 4,050 of them could be detected early. However, 194,550 individuals would receive a false-positive screening. After confirmatory EUS testing, the number of deaths averted by screening exceeds screening-related deaths by a ratio of 1.5:1 (Table 1). However, the number of resulting major morbidities due to screening is still greater than the number of deaths averted by a ratio of 1:4.3. With our near-perfect 99.9% test in a highly specific population, we can achieve a 23:1 true to false-positive ratio after EUS testing and a ratio of deaths averted to deaths caused of 9.4:1 (Table 1). Even still, the ratio of individuals helped by early detection only slightly exceeds those harmed with a ratio of 1.3:1, far from approximating the ratios of commonly used screening tests. Additionally, this example assumes we are able to correctly identify the 1.95 million individuals with high-risk genotypes. The population-based screening required to identify these individuals would carry its own false positivity rate, increasing the number of healthy individuals harmed. Even with our nearly perfect test, if we increased the risk of pancreatic cancer in a cohort of patients by 9,900 times to an incidence of 99%, this only allows us to improve our ratio of deaths averted to deaths caused by screening to a ratio of approximately 10:1. In fact, no increase in the incidence of pancreatic cancer can fully overcome the resultant harm from the increased number of individuals undergoing pancreatic surgery. This exemplifies the difficulty in using personalized screening based on symptoms or genetic risk.

Pancreatic cancer research spending emphasizes early detection and underfunds surgical innovation opportunities

In 2019, the NIH reported $219 million in research funding in pancreatic cancer (35). Of cancer subtypes that meet the reporting threshold of spending greater than $500,000, pancreatic cancer ranked seventh out of 11 ranked subtypes (Table 2). Whereas many other cancer subtypes saw a decrease in funding between 2018 and 2019, pancreatic cancer saw increases of $4 million.

The NCI Clinical Trials and Translational Research Advisory Committee identified four research initiatives for pancreatic cancer. These initiatives included: (i) understanding the biological relationship between PDAC and diabetes, (ii) evaluating longitudinal screening protocols for biomarkers for
early detection of PDAC and its precursors, (iii) studying new therapeutic strategies in immunotherapy, and (iv) developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways (36). Spending for Initiative 2 far outstripped the other initiatives in all spending years for which data were available (Fig. 2). Reported research initiatives in breast (37) or colon cancer (38) did not include screening or early detection in funding priorities.

When considering NIH-funded grant spending across all fiscal years, spending on pancreatic cancer research demonstrated a higher percentage of total spending on early diagnostic initiatives than breast or colon cancer (Fig. 3A). Additionally, despite worse outcomes from pancreatic cancer surgery when compared with breast or colon cancer surgery, pancreatic cancer demonstrated a smaller percentage of overall funding focused on improving surgical outcomes or techniques (Fig. 3B).

### Pancreatic cancer clinical trials focus on early detection

Pancreatic cancer clinical trials show a similarly greater focus on early detection and underfunding of surgical innovation as compared with breast or colon cancer. At the time of access, there were 2,695 clinical trials listed for pancreatic cancer, as compared with 1,751 clinical trials for colorectal cancer and 9,990 trials for breast cancer. When considering trials performed in the United States, a greater percentage of pancreatic cancer trials were focused on early detection when compared with colon or breast cancer (13.5% vs. 9.2%, 5.4%; Fig. 3C). Similar to our findings in NIH-funded research, pancreatic cancer clinical trials also showed a lower percentage of trials focused on surgical innovation or outcomes improvement (1.9% vs. 4.7%, 4.4%; Fig. 3D).

### Discussion

These examples demonstrate the difficulties in development of a screening test for a disease with low prevalence. Both realistic and highly optimistic examples result in low chances a positive test equates to a positive diagnosis and have harm rates greater than or approaching cure rates. It is clear when considering a disease with low prevalence, designing a more perfect test does not result in improved ability to create an acceptable screening test.

If we examine cancers with currently available screening tests, we find they have characteristics making them more favorable for screening than pancreas cancer. These cancers have higher incidence and therefore higher prevalence. In many cases, the population of interest can be limited resulting in an increased prevalence in the screened group. Breast, cervical, and prostate cancers, for example, are sex specific so the population at risk is decreased by 50%. Ninety percent of lung cancer occurs in patients with a history of smoking, so screening can likewise be limited. Colon cancer is similar to pancreas cancer in that the general population is at risk; however, colon cancer has a higher incidence. In addition, colon cancer has a known precursor lesion that can be removed via a low morbidity and mortality procedure, endoscopic

### Table 2. NIH spending by categories (in millions).

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Figure 2.
NIH-ranked spending by pancreatic cancer funding initiative.

Figure 3A. NIH-ranked spending by pancreatic cancer funding initiative.
polypectomy, reducing the risk of it progressing to cancer. There is some evidence that intraductal pancreatic mucinous neoplasms and pancreatic intraepithelial neoplasms may represent pancreatic cancer precursor lesions that could be targeted for screening (39), but the risk of cancer progression is not well known and there is no low-risk method of treatment.

Ninety percent of pancreatic cancer cases are sporadic, limiting our ability to identify an at-risk population that could benefit from screening. Limiting testing to individuals with known familial risks can, at best, identify 10% of cases, not enough to make a significant improvement in outcomes. Even within a highly selected cohort, significant morbidity and mortality would result in healthy individuals due to the complications associated with pancreatic resection.

Limiting our screening pool based on symptoms, as has been proposed in a model of screening new-onset diabetics, also cannot result in the development of an effective test. As we demonstrated, even for patients presenting with novel-at-risk condition associated with a nearly 10,000 times increase in pancreatic cancer occurrence, we were unable to achieve an increase in survival that would offset the resultant morbidity from an increase in pancreatic surgery. With only minimal gains in survival with both realistic and optimistic models of screening tests in population-based and high-risk cohorts, significant morbidity and mortality in healthy individuals exceed or equal the gains in survival.

Although development of a screening tool for pancreas cancer that could be applied to the general population and identify early-stage, resectable cancers is laudable, the development of a test that would be acceptable to the general population is an insurmountable goal without first making huge strides in improving treatment outcomes.

We conclude that greater attention of the pancreas cancer research community should be focused on improving the outcomes of pancreas cancer treatment, not only increasing survival, but also decreasing morbidity. Once improvements in treatment outcomes have been achieved, the potential for an acceptable screening test could be readdressed. Surgery remains the only treatment potentiating long-term survival in pancreas cancer patients; however, only 20% of pancreas cancer patients are candidates for surgery (23). Focusing research energy on methods and therapies to increase the number of patients who are surgical candidates and improving surgical outcomes seems a better use of limited resources when compared with pursuing a screening test for pancreas cancer that will ultimately lead to more harm than benefit.

Authors’ Disclosures

No disclosures were reported.
Authors’ Contributions

K.E. Caldwell: Conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft, writing—review and editing. A.P. Conway: Data curation, formal analysis, and investigation. C.W. Hammill: Conceptualization, supervision, visualization, methodology, writing—original draft, writing—review and editing.

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