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Editorial

EDITORIAL

Circulating Biomarkers to Identify Patients With Resectable Pancreatic Cancer

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In this issue of the Journal, Killary et al. evaluate a plasma biomarker combination (CA19-9, tissue factor pathway inhibitor [TFPI], and an isoform of tenascin C [TNC-FNIII-B]) for its ability to distinguish patients with early-stage pancreatic cancer from controls (1). The authors previously reported their initial experience evaluating these biomarkers (2). The authors' study design had several strengths, including the use of multiple disease control groups, blinded analysis of samples, and multiple rounds of validation. The authors found their biomarker panel worked best when compared with controls without pancreatitis or diabetes, finding it could distinguish patients with low-stage pancreatic cancer from healthy controls with an accuracy of 82% (compared with 69% for CA19-9 alone, corresponding to 81% sensitivity, 84% specificity).

It is important to evaluate biomarker performance in patients with chronic pancreatitis because biomarkers elevated in patients with pancreatitis are often also elevated in patients with other similar inflammatory conditions. It is also very helpful to have a biomarker test able to differentiate patients with usual new-onset diabetes mellitus from those whose diabetes is pancreatic cancer associated. Indeed, patients with new-onset diabetes are one of the recognized target populations for early detection. One population-based study estimated that 0.8% of patients age 50 years or older presenting with new-onset diabetes mellitus will be diagnosed with pancreatic cancer within three years (3). Identifying patients with new-onset diabetes is a challenge because many do not present with diabetes symptoms and so determining the onset of diabetes is often not possible, but identifying those patients whose new-onset diabetes is related to pancreatic cancer may represent an opportunity for early detection (4). Patients with adult-onset diabetes often have other metabolic comorbidities such as metabolic syndrome, obesity, cardiovascular disease, and sleep apnea; the poorer diagnostic performance of the Killary et al. biomarker panel in patients with diabetes may reflect nonspecific biomarker behavior that would limit its diagnostic performance (5).

Several other studies have identified circulating (6–11) or urine (12) biomarkers that add to the diagnostic performance of CA19-9. Most of these biomarker combination tests have not yet undergone sufficient rounds of blinded biomarker evaluation to evaluate performance in likely target populations, but these tests will probably not have sufficient diagnostic specificity for clinical use as an early detection test. One biomarker thought to have high biological specificity is circulating mutant DNA (13). The challenge is developing a test that can accurately and reliably distinguish true mutations at low concentrations from assay false positives (14).

What performance characteristics are needed for a clinically useful pancreatic cancer screening test? Such a test requires very high diagnostic specificity (>95%) to avoid generating too many false-positive tests. If a hypothetical biomarker blood test were available with outstanding diagnostic characteristics (95% specificity when applied to its target population and 80% sensitivity for detecting stage I pancreatic cancer) and if it were applied to a population of 10 000 new-onset diabetics older than age 50 years with an estimated pancreatic cancer prevalence of 0.8% (3), 64 individuals with positive tests (true positives) could proceed with further diagnostic evaluation (eg, pancreatic CT scan and pancreatic endoscopic ultrasound [EUS]) to diagnose their pancreatic cancer, 16 would have false-negative blood tests (their pancreatic cancer would go undetected), and 500 would receive a false-positive test and have to undergo multiple additional tests before pancreatic cancer could be ruled out. Although other risk groups for a pancreatic cancer screening test (individuals age 55 years or older with multiple first-degree relatives with pancreatic cancer or carriers of an inherited pancreatic cancer susceptibility gene mutation [15,16]) have a higher cumulative lifetime risk of developing the disease than

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new-onset diabetics (which in affected individuals is a manifestation of their pancreatic cancer), their likelihood of having pancreatic cancer at any one screening period is lower and should ideally have a test with even better diagnostic performance characteristics.

One of the particular challenges a screening test to detect pancreatic cancer has to account for is the time window for early detection. Current pancreatic imaging tests can detect many pancreatic cancer masses of 5–10 mm diameter (some cancers are not detectable until they are larger). Because most 2 cm diameter pancreatic cancers have spread to local lymph nodes, the opportunity to detect the most curable pancreatic cancers (those between 5 mm and <2 cm diameter) may be only one or at most two years (at least until improvements in pancreatic imaging allow for the detection of smaller cancers) (17). The challenge involved in detecting very small pancreatic cancers (~1 cm or less) is not limited to pancreatic imaging tests; circulating biomarkers face this challenge too. The diagnostic sensitivity of a circulating biomarker generally increases with tumor burden. Mathematical modeling predicts that a cancer cell mass of several billion cells is needed to raise a typical circulating tumor biomarker level above normal (18). For this reason, many circulating biomarkers do not have sufficient diagnostic sensitivity to identify very small cancers. Studies of cohorts find CA19-9 elevations in a minority of patients' prediagnostic blood samples only within one or two years of diagnosis (and many of these patients may already have advanced disease) (9).

Early detection strategies currently used clinically employ pancreatic imaging (EUS, MRI) firstline for individuals with a sufficiently elevated familial/inherited risk of pancreatic cancer. One advantage of using pancreatic imaging tests is that in addition to being better able to detect low-stage cancers (19), pancreas precursor lesions can also be identified (20,21), potentially enabling intervention to prevent the development of pancreatic cancer. EUS sampling of the pancreas (pancreatic juice [22], fine needle aspirates [23]) can be used to detect biomarkers of cancer or precancerous lesions not identifiable by imaging. Determining the nature and extent of any precancerous changes in the pancreas may help predict those patients most likely to progress to pancreatic cancer, but we need better tests. One reason is that these tests still do not reliably detect microscopic pancreatic intraepithelial neoplasia (PanIN). A test that could detect PanIN, especially PanIN-3, would be very valuable, although it is recognized that detecting and treating precursor lesions brings with it the potential for overtreatment. Further research is needed to determine which early detection strategies will be most successful.

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Note

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