



Liquid biopsy-based biomarkers for early detection of pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related mortality in both men and women in the United States (1). Alarming, the incidence of PDAC-related mortality continues to rise and PDAC is projected to be the second deadliest cancer in the U.S. by 2030 (2). Most PDAC patients are inoperable at diagnosis, leading to a dismal 5-year survival rate of 8.5% (3). Substantial evidence points to the importance of diagnosis of PDAC at an earlier, resectable stage for improved outcome (4,5). Unfortunately, diagnosis of PDAC at an early stage is uncommon and usually incidental, with a majority of patients (~85%) presenting with locally advanced or metastatic disease (6). It is therefore beneficial to identify early-stage PDAC and its precursors that are destined to develop into aggressive disease PDAC (3).

Currently, no clinical marker(s) are available that exhibit the desired performance characteristics for the detection of early stage PDAC among asymptomatic individuals. The use of CA19-9 as a screening biomarker is limited by its reduced performance in pre-diagnostic stages of the disease (7-9), and its lack of expression in ~10% of subjects with fucosyltransferase deficiency (10). Consequently, there is a critical need for additional markers that display collectively higher sensitivity and specificity for reliable detection of early-stage PDAC. In this context, blood-based biomarker(s) represent a relatively non-invasive and cost-effective method for PDAC detection.

In a recent publication by Mellby and colleagues (11), the authors utilized an antibody microarray approach consisting

of 349 human recombinant single-chain variable fragments directed against 156 proteins to develop a biomarker signature for early-stage PDAC. Serum samples consisted of 443 PDAC cases (16 stage I, 132 stage II, 65 stage III and 230 stage IV) and 888 non-PDAC controls (NCs). Data was analyzed using a leave-one-out cross-validation strategy. Two biomarker signatures were defined using the backward elimination algorithm for the classification of (I) NCs versus stage I and II PDAC cases and (II) NCs versus stage III and IV PDAC cases. The resulting models yielded receiver operating characteristic (ROC) area under the curve (AUCs) of 0.96 and 0.98, respectively, for distinguishing PDAC cases from NCs. In order to obtain the optimal predictive accuracy in a validation study, the highest ranked biomarkers were combined and a consensus signature consisting of 29 biomarkers was derived. The 29-marker panel was subsequently validated in an independent cohort consisting of 143 PDAC cases (15 stage I, 75 stage II, 15 stage III and 38 stage IV) and 219 NCs, which yielded an AUC of 0.96 with a specificity/sensitivity combination of 95%/93% in distinguishing stage I and II from NCs. Of note, the authors found that classification performance was not confounded by diabetic status or presence of jaundice (11). The independent validation performed by the authors strengthens the significance of the findings and the potential of the marker panel to identify early-stage PDAC.

The study by Melby *et al.* has some limitations. It is important to recognize that the current biomarker panel was assessed in retrospective case-control cohorts, with

cases consisting of subjects diagnosed with the disease and with controls being predominately healthy subjects. Implementation of a marker panel to screen healthy subjects without known risks for PDAC requires exquisite specificity given the low prevalence of PDAC. At present a marker panel for PDAC would be best suited for screening programs targeting high-risk subjects that include individuals over age 50 years with new-onset diabetes mellitus, asymptomatic kindred of high-risk families, subjects with chronic pancreatitis, and subjects with pancreatic cysts (5) notably intraductal papillary mucinous neoplasm (IPMN), a type of pancreatic cyst commonly detected among asymptomatic patients (5). Currently, the international consensus guidelines recommend resection of IPMN with high risk of malignancy (12). Based solely on radiologic and clinical features, the current guidelines have a sensitivity (>90%) yet are hindered by dismal specificity (25–30%) for predicting malignant IPMN as assessed by surgical pathology (13,14). Moreover, a recent analysis of four U.S. studies demonstrated that 35% of cystic mucinous neoplasms (primarily IPMN) met surgical indications and 13.9% became invasive cancer during one to three years of surveillance (15). Therefore, there is a critical unmet need for biomarkers that predict the likelihood of malignant progression. The performance of the 29-marker panel in distinguishing PDAC from benign or borderline IPMN in the validation cohort was based on a relatively small number of samples (n=13) and therefore would require further assessment in a larger number of samples. In the same context, the application of a blood-based biomarker panel as a screening tool to identify individuals at high risk of developing or actively harboring PDAC even when restricted to at-risk populations is contingent upon the specificity of the markers for PDAC, as compared to other conditions to avoid false-positives as may result from the inclusion of markers such as interleukin-13, -4, and -6, and complement factors C3, C4 and C5 in the panel which are not specific to PDAC (16-19).

Conversely, while the overall performance of the biomarker panel described by Mellby and colleagues yielded a good AUC, there is still room for improvement. There is a need to critically test the relative contribution of different types of biomarkers (e.g., ctDNA, autoantibodies and metabolites) to enable the development of an optimal biomarker combination for the desired clinical application (20). Recently, we demonstrated that the combination of a 5-marker metabolite panel in combination with a previously validated 3-marker protein panel yielded

statistically significantly improved AUC performance relative to the 3-marker protein panel or CA19-9 alone, in a blinded validation cohort of 38 resectable PDAC cases and 82 matched healthy controls (21,22). These findings demonstrate that the combination of different biomarker types has the potential to yield superior results relative to a single biomarker type (23-25).

In conclusion, the panel derived by Mellby and colleagues provides optimism for identifying PDAC at early-stage of disease. However, vigorous and repeated sequential validation in prospective cohorts will be required to fully determine the utility of this biomarker panel in comparison with other previously described and validated markers. Such an undertaking requires a collective effort by stakeholders.

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