Presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, Lake Tahoe, NV, June 18-21.

Prospects for developing a biomarker panel for accurate detection of pancreatic adenocarcinoma. Matthew A. Firpo, Kenneth M. Boucher, Sean J. Mulvihill. University of Utah, Salt Lake City, UT

Most patients with pancreatic adenocarcinoma (PA) present after the disease has advanced to an incurable stage. Screening for PA would likely improve outcomes through earlier detection, but could result in unacceptable levels of false-positive diagnoses using current biomarkers. Recent efforts to identify individual biomarkers or biomarker panels have been disappointing. Furthermore, it is unlikely that an individual biomarker will provide sufficient accuracy for detection of PA given the high amount of molecular heterogeneity in the disease. We propose a novel, intuitive panel design that allows for diverse biomarker selection for accurate diagnosis. Using characteristics of nine PA biomarkers measured in human sera to model the behavior of biomarker panels, we delineate the number of biomarkers required for accurate detection of PA in our panel design.

Levels of AXL, CA 19-9, haptoglobin, hyaluronic acid, MMP-7, MMP-11, osteopontin, serum amyloid A, and TIMP-1 were measured in sera from 117 healthy control subjects and 58 chronic pancreatitis patients, and 159 PA patients prior to treatment.. Threshold indicators were constructed for individual biomarkers at the 95th percentile of the control value. We modeled the behavior of a biomarker panel consisting of a sum of indicator variables, then chose a cutoff for the sum to force specificity to be high, and calculated the resulting sensitivity. To generate correlated biomarkers, we simulated correlated continuous biomarker data, made a 95th percentile cutoff for each biomarker, and then assessed performance as above.

Between 17% and 75% of the PA cases had values above the 95th percentile of control values with an average sensitivity for all biomarkers of 32%. The correlation between the indicator variables was near zero in controls and slightly positive in PA cases. None of the biomarkers were highly correlated. The model shows that a panel consisting of 40 biomarkers characterized individually by 32% sensitivity at 95% specificity would require any 7 biomarkers to be above the threshold and would result in a panel specificity and sensitivity of 99% each. The addition of correlation assumptions reduced sensitivity for the 40 biomarker panel to 94% at an average correlation of 0.05 and 84% at an average correlation of 0.15.

Our modeling shows that a highly accurate, blood-based PA diagnostic panel can be developed from a reasonable number of individual serum biomarkers that are relatively weak classifiers when used singly. The model provides a framework for maximizing biomarker sensitivities and minimizing biomarker correlation. A panel constructed as described is advantageous in that a high level of specificity can be forced and allows for heterogeneity among patients and their tumor characteristics.