Early detection of pancreatic cancer using 5-Hydroxymethylation profiles in plasma-derived cell-free DNA

Anna Bergamaschi, David Haan, Micah Collins, Gulfem Guler, Melissa Peters, Lauren Gigliotti, Shimul Chowdhury, Wayne Volkmuth, Samuel Levy

Bluestar Genomics, San Diego CA, 92112

Background
Pancreatic cancer is one of the deadliest cancers, with approximately 15-20% of patients who present at diagnosis with a resectable disease. The major barrier to better outcomes is the lack of early-detection molecular tools to enable timely intervention. We have developed a test that enables the detection of pancreatic cancer from a simple blood draw. The test incorporates a novel, genome-wide sequencing-based epigenomics detection method that enriches for DNA loci that undergo active de-methylation. The measurement of 5-hydroxymethylcytosine (5hmC) provides a unique and stable biomarker for the early detection of cancer including pancreatic cancer.

Methods
Whole-blood was obtained from a training cohort of 660 individuals (consisting of 132 pancreatic cancers (PaCa) and 528 non-cancers) and a validation cohort of 2,150 individuals (consisting of 102 PaCa and 2,048 non-cancers). Cell-free DNA (cfDNA) was isolated from plasma from which 5hmC and whole-genome libraries were generated and sequenced. Logistic regression algorithms were employed using 5hmC feature sets combined with physical characteristics of DNA fragments to optimally partition cancer from non-cancer samples.

Results
Cross validation of the training model yielded an overall sensitivity of 65.9%,(95% CI, 57.2%–73.9%), early-stage (stage I-II) sensitivity of 57.1% (95% CI, 44%–69.5%) and a specificity of 98%. The model was further validated in a separate, non-overlapping set of blinded and independently processed samples and yielded an early-stage sensitivity of 68.3% (95% CI, 51.9%–81.9%) and a specificity of 96.9% (95% CI, 96.0%–97.6%).

Conclusion
Our results demonstrate that plasma-derived cfDNA 5hmC profiles enable the accurate detection of early-stage PaCa, providing a valuable non-invasive tool especially for those individuals at high risk for the disease, including individuals with genetic predisposition and newly diagnosed type 2 diabetes. A larger clinical study (NODMED - NCT05188586) is ongoing and will provide clinical validation for the detection in individuals at high risk for this deadly disease.