Multi-cancer early detection (MCED) using a blood test represents a rapidly emerging, potentially transformative advance in preventive oncology. Given the complexity of carcinogenesis across organs, simultaneous analysis of multiple biomarkers has the potential to maximize clinical performance, particularly for early-stage tumors.

Previously, we demonstrated the performance of blood tests that incorporated the detection of DNA mutations plus proteins and combining DNA methylation and proteins, respectively. In the original abstract, we described the Training and Validation of 3 biomarkers (aneuploidy, DNA methylation, proteins) using stratified 5-fold cross-validation.

In this presentation, we also included an independent test set and assessed the combination of 4 biomarkers (aneuploidy, DNA methylation, mutations, and proteins).

To assess aneuploidy, we developed a modified version of the Reproductive Element Aneuploidy Sequencing System (REALSeq) blood test.

DNA methylation testing was performed on a refined panel of markers using the Target Enrichment Long-prborne Quantitative Amplified Signal (TELEAS) assay on bisulfite-converted DNA.

A high-throughput platform was used to quantify six extensively-documented protein biomarkers.

Mutation testing was performed using a modified version of the sequencing technology described by Cohen et al.

To assess biomarker performance, we designed a retrospectively- assembled, case-matched feasibility study. The cancers were from all stages and up to 15 organ sites. The non-canncer control cohort was comprised of age-matched presumed-healthy individuals as well as an enriched fraction of samples from individuals with non-cancer diseases. Blood samples were collected in Lilgard® tubes and obtained through different prospective collections and vendor sources.

First, a training and validation set was analyzed including a total of 2388 samples. The early-stage cancers included were breast (59), bladder (23), colon (61), esophageal (44), kidney (41), liver (40), ovarian (30), pancreatic (64), prostate (25), and lung (86). The cancer-specific sensitivity was 97.1% (95% CI: 96.3%-97.9%) for all stages, and specificity was 98.7% (95% CI: 98.3%-99.2%).

Using a diverse set of analytes, we believe that a single blood test has the potential to robustly detect earlier-stage disease in multiple cancer sites.

A larger, prospectively-collected case-control study is underway to further evaluate these results. This will be followed by a very large, prospective, randomized, interventional trial to demonstrate assay performance in an average risk population.

References:

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Disclosure: Christopher Douville is an inventor on some technologies. Licenses to these technologies are or will be associated with equity or royalty payments to the inventors as well as to Johns Hopkins University, being managed by Johns Hopkins Innovation. The terms of all these arrangements are or will be managed by Johns Hopkins University in accordance with its conflict-of-interest policies.

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Multi-cancer early detection through evaluation of aneuploidy, methylation, mutation, and protein biomarkers in plasma

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Figure 1. Diagram illustrating the full cohorts, analyzed samples, and sub-set analyses

Figure 2. Sensitivities of Test Set by Stage for 3- & 4-Marker panel

Table 2. Performance of Test Set for 3- & 4-Marker panel

Table 1. Demographics and Clinical Data of Test Set

Conclusions:

The combination of aneuploidy, DNA methylation, mutation, and protein biomarker classes provide complementary and highly-specific components for a multi-cancer early detection test.

In a training and validation set as well as hold out test set, cancers from all organ types and across all stages could be detected.

The addition of mutation data improved sensitivity across stages with the largest improvement in stage I and stage II cancer detection.

Using a diverse set of analytes, we believe that a single blood test has the potential to robustly detect earlier-stage disease in multiple cancer sites.

A larger, prospectively-collected case-control study is underway to further validate these results. This will be followed by a very large, prospective, randomized, interventional trial to demonstrate assay performance in an average risk population.