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

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Feb 15 2018 1228587319254-403

Background

- 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 proteins1-2 and combining DNA methylation and proteins, respectively3-4.
- In the original abstract, we described the Training and Validation of 3 markers (aneuploidy, DNA methylation, and protein) 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).

Methods

- To assess aneuploidy, we developed a modified version of the Repetitive Element Sequence Identifier (RESI) software.
- DNA methylation testing was performed on a refined panel of markers using the Target Enrichment Long-reading Quantitative Amplified Signal (TELOSA) assay on 1132 samples.
- 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-control feasibility study. The cancers were from all stages and up to 15 organ sites. The non-cancer 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 LBBatm tubes and kept at -80°C until analysis.

Results

- First, a training and validation set was analyzed including a total of 2386 samples. Twelve organ sites included in this set were breast (59), bladder (23), colon (61), esophageal (34), kidney (41), liver (40), lung (86), ovary (30), pancreatic (94), prostate (49), stomach (28), and uterine (40). Three marker classes (aneuploidy, methylation, and protein) were tested for each organ site.
- Second, an independent test set of 1132 samples was analyzed using the models, specifically and thresholds defined in the training and validation set for the aneuploidy, methylation, and protein biomarkers. These 12 organ sites and all stages were used for the analysis. Blood samples were collected in LBBatm tubes and kept at -80°C until analysis.

Table 1. Demographics and Clinical Data of Test Set

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total-Analyzed</th>
<th>Cancers</th>
<th>Non-Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>67.9 (95% CI: 64.0-71.8%)</td>
<td>356</td>
<td>320</td>
</tr>
<tr>
<td>II</td>
<td>68.3 (95% CI: 64.5-72.0%)</td>
<td>310</td>
<td>276</td>
</tr>
<tr>
<td>III</td>
<td>71.0 (95% CI: 66.9-75.0%)</td>
<td>170</td>
<td>147</td>
</tr>
<tr>
<td>IV</td>
<td>75.4 (95% CI: 71.0-79.2%)</td>
<td>145</td>
<td>119</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markers</td>
<td>98.8 (95% CI: 97.3-99.7%)</td>
<td>53.4 (95% CI: 49.6-57.8%)</td>
</tr>
<tr>
<td>3 Markers</td>
<td>98.2 (95% CI: 97.2-99.3%)</td>
<td>61.0 (95% CI: 59.8-63.5%)</td>
</tr>
</tbody>
</table>

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

Figure 3. Analysis Specificity %

References


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Acknowledgements: The study was sponsored by Exact Sciences Corp., Madison, WI. Medical writing and editorial support was provided by Carolyn Hall, PhD, and Feyza Sancar, PhD (Exact Sciences, Madison, WI).

Disclosures: Christopher Douville is an inventor on some technologies. Licenses to these technologies may be sold to third parties by Exact Sciences. Authors have no other disclosures.

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