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Use Of Glycoproteome Profiles To Detect Advanced Adenomas And Colorectal Cancer

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Introduction

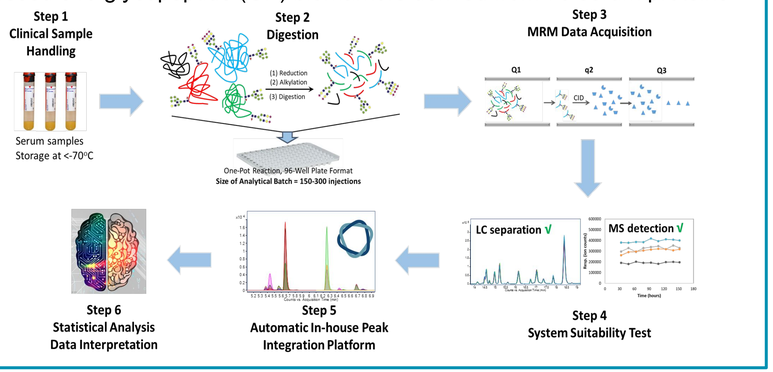
Colorectal cancer (CRC) remains a very prevalent cancer despite current screening modalities. Precancerous lesions, or advanced adenomas (AA), commonly precede invasive cancer development by a number of years.

Glycosylation is one of the most ubiquitous and functionally important forms of post-translational modification. InterVenn has built a novel platform that combines liquid chromatography-mass spectrometry (LC-MS) with a proprietary, artificial-intelligence-based data processing engine, allowing for highly scalable and reproducible quantification of glycoproteins with site- and glycan-specificity.

To detect glycoproteomic profiles associated with the occurrence of AA/CRC, we studied serum glycoproteins in 563 patient samples: 196 healthy controls, 88 ulcerative colitis (UC) controls, 32 AA, and 247 CRC.

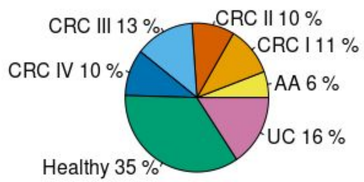
Analytical Workflow

Assessed 519 glycopeptide (GP) biomarkers derived from 70 serum proteins



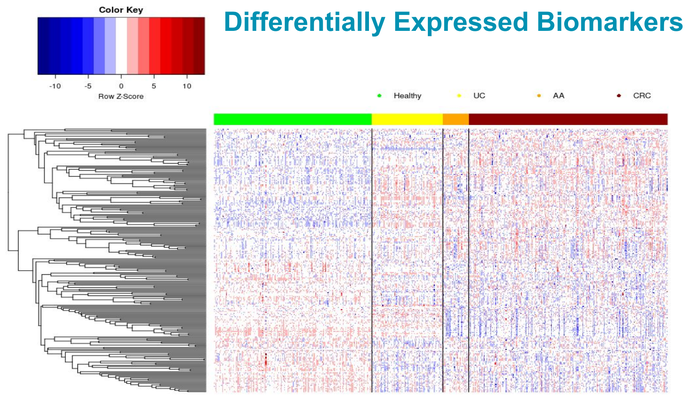
Demographics

- **563 samples sourced from biorepositories**
- **Mean age: 57 years (range: 19 – 94)**
- **50% female**



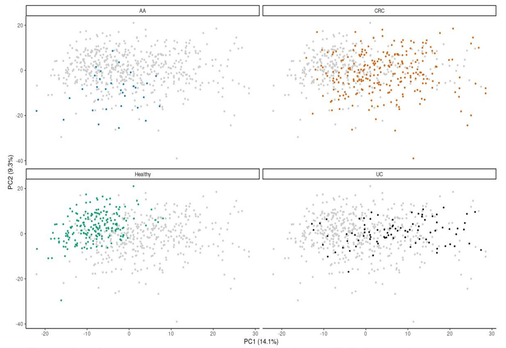
Results

Differentially Expressed Biomarkers



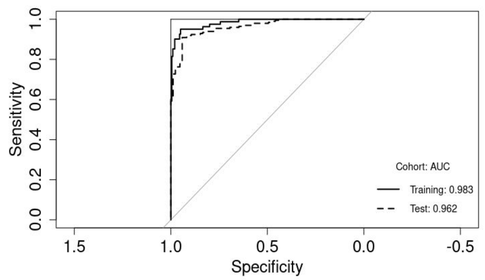
Clustered heatmap of patients (color-coded along the x-axis by their disease indication) for all normalized abundance features that have an FDR<0.05. As indicated above, several potential biomarkers are differentially expressed between CRC/AA patients and healthy/UC controls

PCA by Patient Entity



Principal component analysis (PCA) plot to visualize few important features that exhibit the intrinsic variation among different subgroups

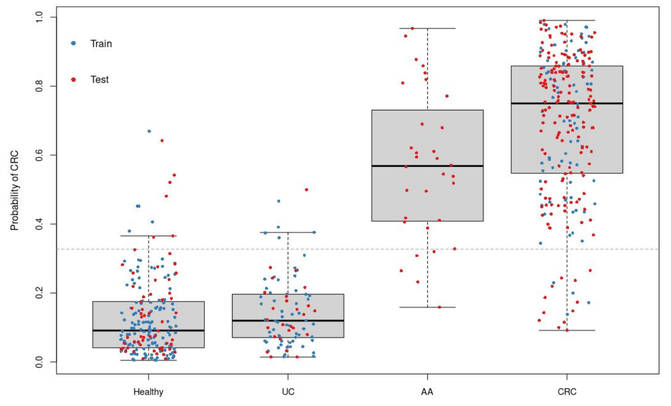
- **Samples were split into a training (50%) and a hold-out test set (50%)**
- **250 differentially abundant glycopeptides/peptides between CRC/AA and healthy/UC controls**



ROC for the comparison of CRC/AA vs. healthy/UC control samples

Modeling

- **Repeated cross-validated Lasso regression yielded a multivariable classifier consisting of six glycopeptide/peptide biomarkers with non-zero coefficients**



Discussion

Predicted probabilities for the training and test samples based on the classifier show increasing severity with disease progression for AAs and CRCs; this indicates a link to the biology of disease. UC samples were included as non-cancerous GI disease controls to correct for non-specific inflammatory signals known to be associated with malignancies.

The model achieved excellent performance in the test set (accuracy=0.92, sensitivity=0.91, specificity=0.92), with AuROCs of 0.98 and 0.96 for training and test sets respectively.
Sensitivity for all stages of CRC was 92.0% (91.2% for stage 1/2, 93.2% for stage 3/4) and 84.4% for AAs.

Future Work

Our results indicate that peripheral blood glycoproteomic profiles of abundant proteins show statistically significant differences among individuals with CRC/AA, and healthy and UC controls. Identification of GPs/peptides patterns in blood serum may be a promising approach to develop an effective non-invasive screening tool for the early detection of AA and CRC.