# Deep Plasma Proteomics for Early-Stage Breast Cancer Detection

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## Clinical Need and Current Guidance

Annual breast cancer screening is a critical piece of women's health but current technologies are less effective in patients with dense breast. The FDA's mandate in 2024 to include a dense breast notification on all mammogram reports has increased patient awareness without a solution.[1-2]

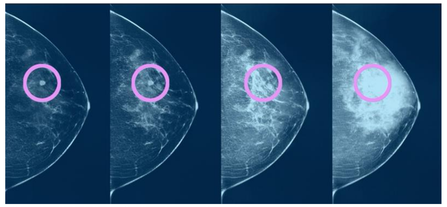



**Figure 1.** Increased breast density decreases mammogram sensitivity.

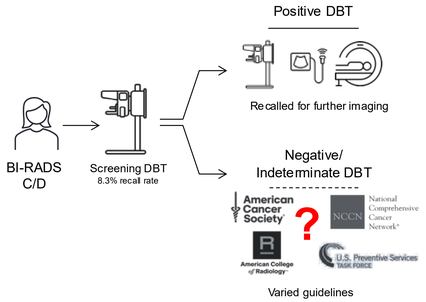



**Figure 2.** Current guidance for women with dense breast tissue and a negative mammogram is highly variable.

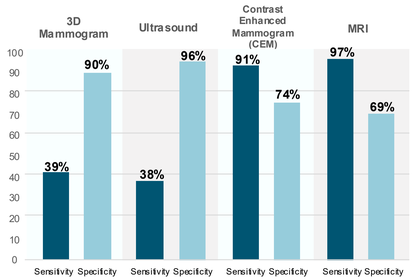



**Figure 3.** Sensitivity and specificity of current imaging technologies.[3-5]

## Blood Based Assays

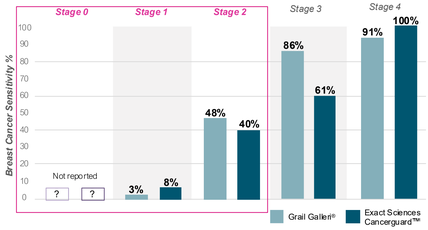



**Figure 4.** Prominent liquid-based biopsies are nucleotide-based assays which currently remain inapplicable to early-stage breast cancer detection.[6-7]

## Proteomic Platform

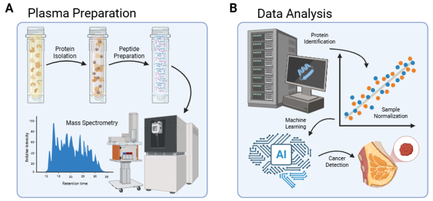



**Figure 5.** Proteins were isolated using magnetic bead-based enrichment and then digested to create peptides. The peptides were loaded onto a C-18 column, eluted over time followed by electrospray ionization into a mass spectrometer in data-independent acquisition (DIA) mode. Peptides were quantified by DIA-NN and then normalized.[8] Created in BioRender.[9]

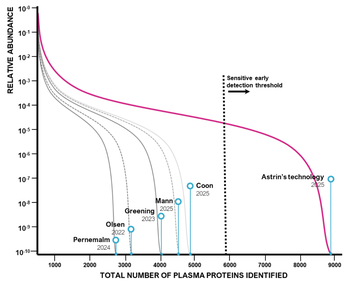



**Figure 6.** Simultaneous innovations in sample preparation, equipment capabilities, and data processing have led to drastic increases in protein depth. With these improvements, proteins that are 8-9 orders of magnitude lower in abundance than common plasma proteins can now be detected.

## Retrospective Study

Biobanked plasma was obtained from 1,259 women classified as either healthy or cancer. The classifier was trained on 845 women, 466 healthy and 379 cancer, and then validated on 397 women, 195 healthy and 202 cancer (70:30 training: validation split). All cancer samples were from newly diagnosed treatment naïve breast cancer patients.

The classification threshold for breast cancer was determined using five-fold cross-validation on the training data, with a target specificity >90%. The model was then retrained on the full training set, and both the model and threshold were locked. Validation samples were blinded and processed separately. The validation samples were then evaluated followed by unblinding of the data to assess validation performance.

### Patient Demographics

**Table 1.** Healthy patients were selected to demographically match the patient population. Samples were randomly assigned to the training and validation sets.

| Characteristics | Training Set | | Validation Set | |
|---|---|---|---|---|
| | Healthy n = 466 | Cancer n = 379 | Healthy n = 195 | Cancer n = 202 |
| Age | | | | |
| Mean (SD) | 55.4 (10.8) | 57.2 (12.4) | 56.4 (8.8) | 59.8 (13.0) |
| BMI | | | | |
| Mean (SD) | 26.2 (4.4) | 27.8 (6.3) | 26.2 (4.3) | 26.7 (5.4) |
| Race, n (%) | | | | |
| White | 429 (92.1%) | 355 (93.6%) | 176 (90.3%) | 197 (97.5%) |
| Black | 12 (2.6%) | 8 (2.1%) | 4 (2.1%) | 1 (0.5%) |
| Asian | 21 (4.5%) | 15 (4.0%) | 10 (5.1%) | 4 (2.0%) |
| Other/ Unknown | 4 (0.8%) | 1 (0.3%) | 5 (2.5%) | 0 (0.0%) |
| Cancer Stage, n (%) | | | | |
| Stage 0 | | 45 (11.9%) | | 13 (6.4%) |
| Stage 1 | | 130 (34.3%) | | 69 (34.2%) |
| Stage 2 | | 152 (40.1%) | | 98 (48.5%) |
| Stage 3 | | 35 (9.2%) | | 16 (7.9%) |
| Stage 4 | | 14 (3.7%) | | 2 (1.0%) |
| Unknown | | 3 (0.8%) | | 4 (2.0%) |
| Source, n (%) | | | | |
| ProteoGenex | 316 (67.8%) | 240 (63.3%) | 105 (53.8%) | 129 (63.9%) |
| BioIVT | 150 (32.2%) | 139 (36.7%) | 90 (46.2%) | 73 (36.1%) |

### Results

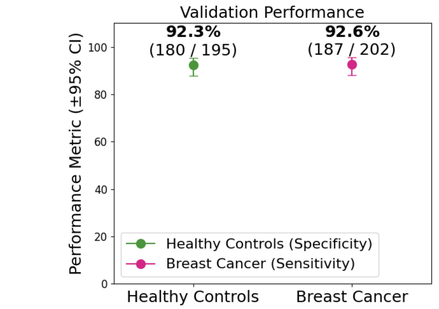



**Figure 7.** The classifier had a sensitivity of 92.3% and a specificity of 92.6% on the validation data set. No demographic confounders were found in either sensitivity and specificity across demographic subgroups.

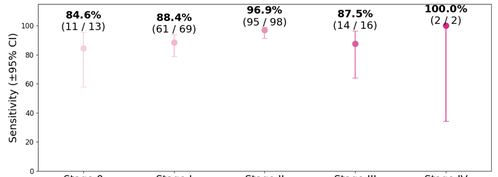



**Figure 8.** Sensitivity remained above 84% even in stage 0 patients.

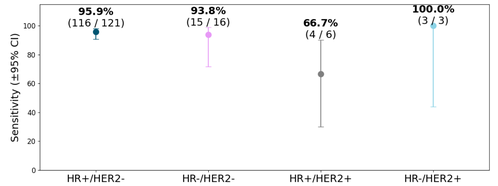



**Figure 9.** Sensitivity remained high across molecular subtypes. Of particular interest, triple-negative breast cancer had 93.8% sensitivity.

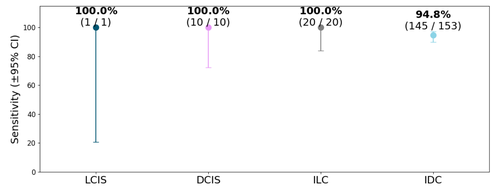



**Figure 10.** Sensitivity remained high across pathological subtypes.

## Ongoing and Future Trials

- Recruitment for a prospective trial at time of biopsy is underway at the Mayo Clinic, Advocate, Baptist MD Anderson, and multiple CRO sites.
- Assessment of early breast cancer detection via the PRISM study of ~4,500 women at the time of screening (with Mayo Clinic)
- Future studies will focus on women with dense breast tissue and collect samples at the time of screening.

## Conclusions and Clinical Impact

Utilizing deep proteomic profiling, we have developed a blood-based assay with high sensitivity for early-stage breast cancer detection, regardless of breast density. Importantly, this assay can provide additional insights for patients with dense breast tissue who receive the FDA mandated dense breast notification on their mammogram report. Additional clinical information can provide reassurance and reduce patient anxiety related to breast cancer probability.

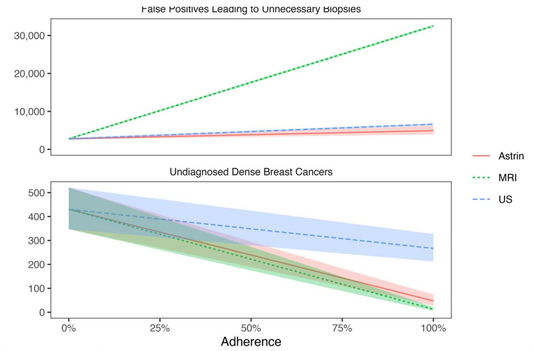



**Figure 11.** This blood-based assay has the potential to drastically decrease unnecessary biopsies while increasing the breast cancer detection rate.

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**Contact Information**

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