

Early Detection Research Network



Breast/Gyn Collaborative Group Update



Key Scientific Advances: Breast Cancer

~840/1,050 patients enrolled into a new prospective mammography study (Marks/Heine)

Anticipated near-term outcomes: Will assess radiomic and blood-based biomarkers to guide biopsy decision making for women with BI-RADS 4 mammograms

Discovery of candidate biomarkers for different molecular subtypes of breast cancer in PDX mouse models progressing well (Paulovich)

Anticipated near-term outcomes: Wealth of data on novel blood-based early detection biomarkers specific to the major molecular subtypes of breast cancer

Profiling of anti-glycosylated protein antibody markers for breast cancer early detection is advancing (LaBaer/Anderson)

Anticipated near-term outcomes: Will discover novel blood-based early detection biomarkers for breast cancer in human samples

Phase 3 validation of autoantibody and proteomic biomarkers in longitudinal preclinical samples for ER+ breast cancer continues (Li)

Anticipated near-term outcomes: Validation of biomarkers that meet pre-specified statistical criteria to meet identified clinical applications

Key Scientific Advances: Ovarian Cancer

7,400+ women enrolled in early detection trial with ~40,000 longitudinal serum samples (Bast/Lu)

Anticipated near-term outcomes: sensitivity for early stage disease 67%, PPV > 50%; second generation algorithm including CA125 and HE4.

Phase 2 validation of 15 autoantibodies, CA125, HE4, CA125 & HE4 antigen-autoantibody complexes (Bast/Anderson/Drescher/Skates)

Anticipated near-term outcomes: Addition of anti-TP53, anti-CTAG increases sensitivity from 70% to 75% at 98% specificity

Key Scientific Advances: Ovarian Cancer

Multivariate Index Assay combining methylomics profiling of ovarian cancer precursors + plasma proteomics (Shih/Wang/Zhang)

Anticipated near-term outcomes: sensitive PCR methylomic tests for STICs, deep learning for biomarker discovery and biomarker panel optimization

Plasma Proteomic Biomarker Discovery in Pre-diagnostic Longitudinal Samples (Skates/Gillette/Birrer)

Anticipated near-term outcomes: 20 novel plasma protein biomarkers rising significantly over time prior to detection, 5 established markers – positive controls

Key Scientific Advances: Ovarian Cancer

Phase 2 study AAb-p53 and CST-derived antigens to SOC, Phase 3 validation in WHI samples (Drescher)

Anticipated near-term outcomes: Novel auto-antibodies biomarkers that complement CA125

tdDNA in Uterine Lavage and Serum proteins for early detection of OC with ultrasensitive Duplex TP53seq, 23 Haloplex_Seq (Breast/GYN Team project)

Anticipated near-term outcomes: Complementarity of cfDNA and serum proteins. Biorepository of PRoBE compliant Uterine Lavage, serum, plasma, buffy coat, cervical brushings, OC tissue / FFPE in RRSO (8/250 enrolled)

Where is the field moving?

- **Multi-cancer early detection (Papadopoulos, Allen)**
 - cfDNA mutations + plasma proteins (JHU)
 - cfDNA methylation (GRAIL)
- **Integration of germline genomics and circulating biomarkers for early cancer detection (Mary Daly)**
- **cfDNA (Patel, Zhou)**
 - methylation (Patel)
 - Methylation + fragment length + CNV + Microbiome (Zhou)
- **Extracellular Vesicles (EVs) (Stott, Lyden)**
 - Spectrum of EVs – field flow fractionation (oncosomes, migrasomes, exophers, exosomes, exomeres)
 - Cargo – proteins, RNA, Lipids, DNA
- **Tumor-associated lymphoid cell compartment (Li, Harismendy)**
 - T-cell repertoire (TCR)
 - DCIS vs. malignant breast cancer
- **Imaging and artificial intelligence (Lo, Mahabal)**
 - Deep learning (AI) for images – detect lesions, classify (malignant/benign), integrate with blood biomarkers
 - Data Driven Science, longitudinal image analysis, virtual reality training

Strengths and suggestions to strengthen the Network

- Multi-omic analyses, including imaging
- Collaborative team science
- Sample sharing
- Emerging technologies
- EDRN Network organization
- Transparency
- Scientific rigor
- Clinical applications
- Biomarker study design covered from start to finish
- A lot of deep knowledge about biomarkers
- Ties to industry

Weaknesses and solutions and strategies for mitigation

- Biomarkers: Lab to clinic
- Low incidence of cancers, heterogeneity – additional challenge
- Biological limitations
- Access to pre-diagnostic samples – ongoing EDRN collection
- Integrating imaging & biomarkers – not strong, but becoming stronger
- Bring in other investigators to early detection – small uptake – possibly due to small amount of funds
- Compete with Google & other large entities – unclear where EDRN's niche is
- Renewal timing: once per 5 years doesn't work – better on/off each year
- Lack of reviewers if once per 5 years
- Health economics of early cancer detection not supported, but essential
- Foster next generation of investigators – K awards not connected with EDRN

Opportunities and prioritized opportunities

- Leverage consortia with biobanks to move markers forward: national and international
- Big data initiatives
- Pre-cancer atlases
- Surgical intervention
- Technology development (AI, TCR, exosomes, methylation, mutations, CNV)
- Large scale validations of assays
- Partner with the Googles of the world
- Change from disease groups to modality groups? Or have both?
- Data and algorithm sharing with outside groups?
- Better marketing of EDRN knowledge base?
- Set benchmarks for successful early detection biomarkers via benefit vs. harm tradeoffs; for individual cancers and pan cancer early detection tests
- Foster next generation of investigators

Threats and mitigations

- IP issues: combining multimodality markers
- Mayo vs Prometheus (lack of IP protection for diagnostics)
- FDA approval: high bars
- Cost of larger studies
- Pan cancer initiatives; tension with focused disease approaches
- Disease silos
- We could be viewed as unnecessary, can R01s do it?
- Size of studies required for FDA validation
- Claims made by large companies about their results – not independently verifiable due to huge scale of studies required

Work facilitated by EDRN's structure/funding

- **Collaborative team projects**
- **Establishment of reference set data and samples for biomarker discovery and validation**

Thank you!

From the EDRN Breast/GYN Collaborative Team

SWOT Analysis

Strengths:

Multi-omic analyses

Collaborative team science / sample sharing

Scientific rigor

Thinking end to end / deep knowledge

Weaknesses:

Translation of biomarkers to the clinic

Access to pre-diagnostic samples

Renewal timing / ability to bring in new investigators

Ability to do pan-cancer work

Insufficient funding for clinical utility trials

Lack of consideration of the economic impact of our work

SWOT Analysis

Opportunities:

Big data initiatives

Partnerships with industry

New technologies

Foster next generation of researchers

Threats:

High bar of FDA approval

High cost / size of studies needed for validation

Other consortia / research groups / industry in this space