



THE 11TH INTERNATIONAL  
**BREAST DENSITY & CANCER RISK  
ASSESSMENT WORKSHOP**

June 4-6, 2025 | Līhu'e, HI



# 2025 PROGRAM

*Photo Credit: Hawaii Tourism Authority (HTA) / Heather Goodman / @hbgoodie*

## Thank you to our sponsors

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This workshop would not have been possible without financial support from our industry and academic partners.

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|                            |        |
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## Day 1 | State of the Art in Risk Assessment and Imaging Biomarkers

June 4, 2025- - - - -page 7

|          |                                                                   |        |
|----------|-------------------------------------------------------------------|--------|
| 6:30 AM  | Registration & Breakfast                                          |        |
| 7:30 AM  | Oli Blessing & Introduction .....                                 | page 8 |
| 8:20 AM  | <b>State of the Art in Risk Assessment and Imaging Biomarkers</b> |        |
| 12:00 PM | Lunch                                                             |        |
| 1:00 PM  | Adjourn                                                           |        |
| 1:30 PM  | Networking Activities                                             |        |

## Day 2 | Breast Density Workshop

June 5, 2025- - - - -page 12

|          |                                                                                                            |                |
|----------|------------------------------------------------------------------------------------------------------------|----------------|
| 7:00 AM  | Breakfast                                                                                                  |                |
| 8:00 AM  | Housekeeping                                                                                               |                |
| 8:10 AM  | <b>Exploring the Biology and Modulators of Breast Density including Hormones, Obesity, and Environment</b> |                |
| 10:50AM  | <b>Breast Cancer Risk Board: An Open Discussion of Cases in the Style of a Tumor Board</b>                 |                |
| 12:00 PM | Lunch                                                                                                      |                |
| 1:00 PM  | <b>Innovative Technology and Methods for Imaging Risk Assessment</b>                                       |                |
| 2:00 PM  | <b>Poster Session 1 (Odd Numbers) .....</b>                                                                | <b>page 24</b> |
| 3:30 PM  | <b>Innovative Technology and Methods (Continued)</b>                                                       |                |
| 4:00 PM  | Adjourn                                                                                                    |                |
| 4:30 PM  | Networking Event                                                                                           |                |

## Day 3 | Breast Cancer Risk Assessment

June 6, 2025- - - - -page 18

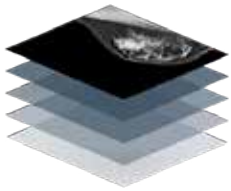
|          |                                                                                                                 |                |
|----------|-----------------------------------------------------------------------------------------------------------------|----------------|
| 7:00 AM  | Breakfast                                                                                                       |                |
| 8:00 AM  | Housekeeping                                                                                                    |                |
| 8:10 AM  | <b>Frontiers in Breast Cancer Risk Assessment: Integrating Clinical, Omic, and Imaging Biomarkers</b>           |                |
| 11:25 PM | Lunch                                                                                                           |                |
| 12:25 PM | <b>Engaging Communities to Improve Risk Models and Screening Strategies Toward Health Quality for All Women</b> |                |
| 1:20 PM  | <b>Poster Session 2 (Even Numbers) .....</b>                                                                    | <b>page 26</b> |
| 2:25 PM  | <b>Engaging Communities (Continued)</b>                                                                         |                |
| 4:15 PM  | Closing Remarks                                                                                                 |                |
| 4:30 PM  | Adjourn                                                                                                         |                |
| 5:00PM   | <b>New Frontiers in Breast Cancer Research and Management (Open to the Public)</b>                              |                |

|                     |          |
|---------------------|----------|
| Course Roster ..... | page 106 |
|---------------------|----------|

# A growing ecosystem for early detection

Powerful software for cancer risk and density assessment

## Volpara Scorecard™



Volpara's software is used to assess breast density of over 15 million women



> 140 million mammography and tomosynthesis images have been deidentified and analyzed by Volpara Health

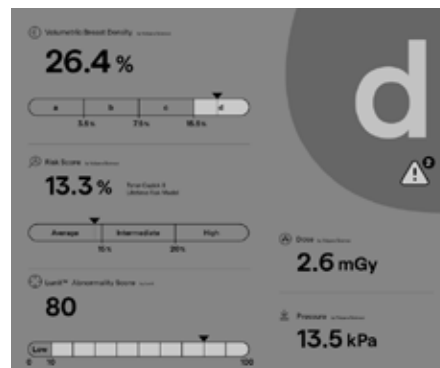


Volpara has the most scientific papers of all breast radiology AI software companies<sup>1</sup>



The only breast density assessment validated for use with Tyrer-Cuzick 8

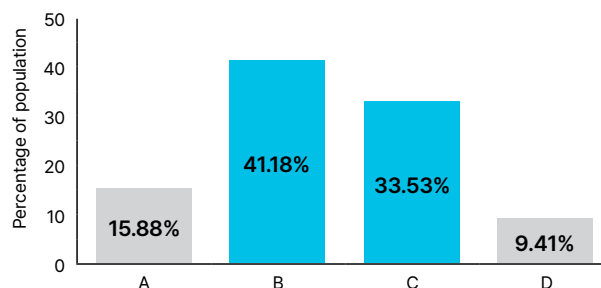
Research has shown that radiologists who assess breast density visually assign density categories inconsistently.<sup>2</sup> The objective TruDensity® algorithm in Volpara® Scorecard™ is proven to reduce reader variability. TruDensity automatically assesses the volumetric breast density percentage (VBD%) of each mammogram on a continuous scale. This differentiates each woman on a continuum of density—whether her density is a “high B” or a “low C.” This gives the radiologist important insight to evaluate patients on the dense, non-dense threshold more precisely.



Radiologists typically agree with Volpara's assessment of non-dense (A or B) or dense (C or D) 96% of the time.<sup>3</sup>

## Accuracy and consistency are critical to patient density classification

**Nearly 75% of patients will be assessed in either the B or C density categories.** Accurate classification between a BI-RADS® B and C is essential.



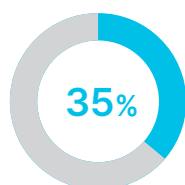
BI-RADS classification of breast density by categories A to D<sup>4</sup>



Two experts agreed about 65% of the time on a BI-RADS density category in a blind study.<sup>5</sup>

## Lunit AI less affected by breast density

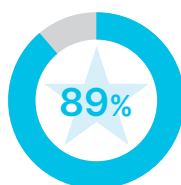
Dense breasts are difficult



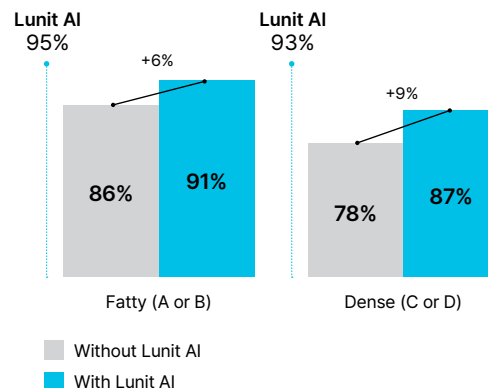
Cancers missed at screening in extremely dense breasts.<sup>6</sup>



Lunit AI sensitivity in dense breasts



Sensitivity in dense breasts.<sup>7</sup>

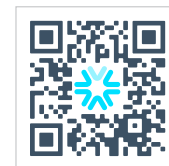
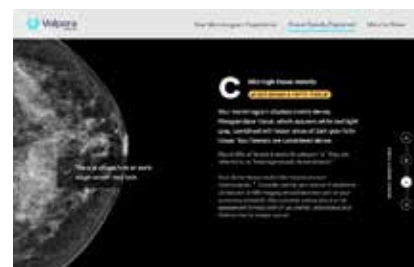


*“Lunit provides peace and confidence reading each case. There is a huge risk of missing cancer. Lunit AI performs well in assisting radiologists with challenging dense breast cases.”*

David Forsberg, MD, Breast Radiologist  
Mosaic Breast Imaging

## Volpara® Thumbnail™

Volpara® Thumbnail™ empowers patients to understand their breast density with image-enhanced mammography results letters. Patients are shown two non-diagnostic images of their breasts and an explanation of what their density category means in simple-to-understand terms and visuals.

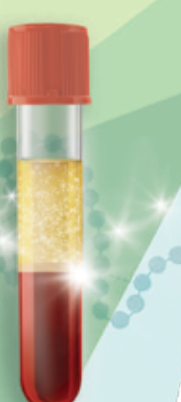


Scan the QR code to learn more.

- <https://link.springer.com/article/10.1007/s00330-021-07892-z>
- Redondo A, Comas M, Macià F, Ferrer F, Murta-Nascimento C, Maristany MT, Molins E, Sala M, Castells X. Inter- and intradiagnostic variability in the BI-RADS assessment and breast density categories for screening mammograms. *Br J Radiol.* 2012 Nov;85(1019):1465–70. doi: 10.1259/bjr/21256379. Epub 2012 Sep 19. PMID: 22993385; PMCID: PMC3500788.
- Data on company file. Analysis from 36,642 cases across four clinics.
- Panta, Ritu & Shrestha, Shanta & Jha, Anamika. (2020).
- Ciatto et al, The Breast 2005. Glandular density distribution in digital mammography. *Grande Medical Journal.* 2: 5–9. 10.3126/gmj.v2i1.45080.
- Hyo Eun Kim, et al., Changes in cancer detection and false-positive recall in mammography using artificial intelligence: a retrospective, multi reader study, *The Lancet Digital Health*, 2020.
- Hyo Eun Kim, et al., Changes in cancer detection and false-positive recall in mammography using artificial intelligence: a retrospective, multi reader study, *The Lancet Digital Health*, 2020.

# SENSITIVE. SPECIFIC. CERTITUDE.

Introducing *Certitude*, Astrin's supplemental screening test poised to revolutionize breast cancer detection for women with dense breasts—all with a simple blood draw.



*Certitude* employs Astrin's patented, proprietary, deep proteomic platform to differentiate healthy patients from early-stage breast cancer patients using a small blood sample.

*Certitude* will dramatically improve accuracy in identifying patients who need further screening, reducing unnecessary referrals for costly, more invasive tests. Preliminary trials demonstrate exceptional sensitivity and specificity, exceeding industry standards.



scan here to find out  
more about *Certitude*

  
**Certitude**

Workshop Overview Dense breast tissue is a significant risk factor for breast cancer, and ongoing efforts aim to better understand its implications. Recently, the Food and Drug Administration implemented a regulation in September 2024 that requires healthcare providers to inform women about their breast density status, providing information on whether their density is low or high and how it may impact breast cancer detection and risk. The US Prevention Task Force continues to evaluate the evidence regarding the balance of benefits and harms of supplemental screening for breast cancer using breast ultrasonography or magnetic resonance imaging (MRI) in women with dense breasts. Our understanding of breast cancer risk, especially how it differs by race, environment, body mass index, and other clinical factors, continues to evolve. Breast density alone is an important indicator but just one piece of determining breast cancer risk. It is more important than ever to continue to explore new technologies and methods to extract quantitative risk and masking information from breast images, especially the growing uses of artificial intelligence. For all of these reasons, the study of breast density and risk-based modeling is more relevant than ever.

The International Breast Density & Cancer Risk Assessment Workshop has been held biennially since 2002 and in Hawai'i since 2019. We are delighted to welcome you to the 11th Workshop, now held in Lihue, Kauai. I and my co-chair, Karla Kerlikowske (UC San Francisco), are pleased that so many of you were able to join us this year. Ongoing changes to government funding in the research space have significantly impacted travel and conference attendance this year and your presence shows our shared determination to continue scientific advancement and real-world impact.

In this workshop, we will explore all aspects of the evolving landscape of breast cancer risk factors derived from mammography images. We will examine how these radiomic biomarkers contribute to clinical risk assessments for overall breast cancer risk as well as interval and advanced cancer risk. On day one, grounded with an introductory talk from a local breast cancer patient advocate, we will explore essential data on breast cancer risk assessment, especially as it affects the front line of patient care. Day two shifts to examining how environmental, hormonal, and obesity-related factors intersect with biological determinants of breast density as well as an indepth look into the new innovations in collecting data from breast images. Right before lunch on day two, we will also have the "Breast Cancer Risk Board" where with a panel of experts we can discuss real cases in the style of a Tumor Board. The third day will emphasize integrating risk models with AI and multimodal data in the session before shifting the focus towards the importance of ensuring that these strategies take into consideration all women.

Finally, while in Kauai, we encourage you to take some time to explore the natural beauty of the island. Take a boat tour to witness the majestic Na Pali Coast, hike through the lush mountains to discover why it is called the "Garden Island," or visit the Kauai Museum to learn about the island's unique history. Through your time here, we hope you can be introduced to the people of the islands and how they come from every corner of the world, as well as how cancer has touched many of their lives. Hawai'i is truly the ideal place for the meeting, grounded in the needs of people and the representation of almost all populations. We hope you take this opportunity to get to know Hawai'i, make meaningful connections with your peers, and proudly share your attendance at this impactful meeting.

**Mahalo,**

**John Shepherd - for the Chairs of the Workshop**

—  
The 10th International Breast Density and  
Cancer Risk Assessment Workshop.  
Kona, HI (2023)



## General Information

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### Meeting Room WiFi Access

TBD

**TODO: WiFi info**

### Feedback Survey

At the end of the meeting, we welcome your feedback through our feedback survey here:

<https://breastdensityworkshop.org/feedback-survey>

### Security

We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended anywhere.

### Exhibits

Industry exhibitors will be available in the Salons 2+3 during breakfast, breaks, and lunches. Their tables are throughout the room near the poster sessions and banquet tables.

### Poster Session and Presenter Information

The poster sessions will take place in the Salon 2. Session 1 will be held on Thursday, June 5 for the ODD numbered posters, and Session 2 will be held on Friday, June 6 for the EVEN numbered posters. Please look for your poster number on page 40 or at the bottom of the page with your abstract.

### Final Presentations

A private link to PDF versions of the final presentations will be sent via email 3-4 weeks after the course.

## Conference Committee

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Aimee Bowen

Elizabeth Kuioka



and the Shepherd Research Lab staff.

If you have any questions during the conference, feel free to see one of us!

## Course Chairs

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**John Shepherd, PhD**  
University of Hawai'i Cancer Center



**Karla Kerlikowske, MD**  
UC San Francisco School of Medicine

## Scientific Advisory Committee

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**Kimberly Bertrand, ScD**  
Boston University School of Medicine



**Per Hall, MD, PhD**  
Karolinska Institutet



**Fredrik Strand, MD, PhD**  
Karolinska Institutet



**Rulla Tamimi, ScD**  
Weill Cornell Medical College



**Celine M. Vachon, PhD**  
Mayo Clinic Rochester



### **Carla H. van Gils, PhD**

Professor of Clinical Epidemiology of Cancer  
Julius Center for Health Sciences and Primary Care  
University Medical Center Utrecht

Carla van Gils has been a researcher at the University Medical Center Utrecht since 2001, and a professor of clinical epidemiology of cancer since 2017. Her research work focuses on epidemiological and clinical cancer studies, with a particular focus on prevention, early detection, and risk prediction models. In these studies, she works with imaging, pathologic, clinical, biomarker and risk factor data, in large national and international cohorts. One of her largest studies is the DENSE trial, a Dutch nationwide multicentre randomised trial that shows benefit and cost-effectiveness of MRI breast screening of women with extremely dense breasts. Recently the DENSE-2 trial started, in which she investigates the additional value of abbreviated MRI and contrast-enhanced mammography in women with extremely dense breast tissue. Since June 2021 Carla van Gils is also Director of the Dutch Cancer Society (charity and research funding organization).



### **Gretchen L. Gierach, PhD, MPH**

Director and Senior Investigator, Integrative Tumor Epidemiology Branch  
Division of Cancer Epidemiology and Genetics  
National Cancer Institute

Dr. Gretchen Gierach earned her MPH and PhD degrees in epidemiology from the University of Pittsburgh, PA, with concentrations in cancer epidemiology and women's health. She joined the U.S. National Cancer Institute's Division of Cancer Epidemiology and Genetics (DCEG) as an NCI Cancer Prevention Fellow, continued as a tenure-track investigator, and was awarded scientific tenure from the NIH in 2017. She served as Deputy Director of the Integrative Tumor Epidemiology Branch from 2018 through 2020 and was appointed Director in 2021.

Dr. Gierach leads an integrative epidemiologic research program aimed at advancing understanding of breast cancer etiology and progression through focused investigations of two of the strongest risk factors for sporadic breast cancer among women, namely breast density and hormones. Dr. Gierach has been awarded the NCI Merit Award in Cancer Prevention Research Training and an Award to Advance Research on Cancers in Women from the NIH Office of Research on Women's Health.



### **Professor Boyoung Park, MD, PhD**

Department of Preventive Medicine, Hanyang University College of Medicine

Boyoung Park is a professor in the Department of Preventive Medicine at Hanyang University College of Medicine. Her research interests mainly consist of epidemiological research on cancer, especially breast cancer. Based on national health examination and mammographic breast cancer screening data, her research team has investigated cancer risk factors and associations between changes in risk factors and future cancer risk.

She is a principal investigator of the Korean Atomic Bomb Survivor cohort. Although cohorts of Japanese atomic bomb survivors and their descendants were constructed in the 1950s, right after atomic weapons drops on two Japanese cities, Korean atomic bomb survivors (approximately 100,000 Koreans were estimated to live in Hiroshima and Nagasaki and exposed to atomic bombs) were neglected and not identified to the public until the 1990s. Her research team recruited atomic bomb survivors and their descendants to determine whether exposure to atomic bombs would be inherited from their descendants. Despite a severe bias towards survivorship, her research team has tried its best in the current situation. In addition, she has operated the Epidemiology and Data Management center for the Korean HIV/AIDS cohort.



### **Mary Beth Terry, PhD**

Executive Director, Silent Spring Institute  
Associate Director, Herbert Irving Comprehensive Cancer Center  
Professor, Department of Epidemiology (Env Health)  
Mailman School of Public Health  
Columbia University Irving Medical Center

Mary Beth Terry is a Professor of Epidemiology and Environmental Health at Columbia University. She also serves as the Executive Director of Silent Spring Institute. She has spent the last 25 years focused on environmental modifiers of breast cancer risk, particularly in younger women. She has led multi-generational family cohorts both locally within New York City and globally. She currently has funding through DoD, the Breast Cancer Research Foundation, National Cancer Institute, and the National Institute of Minority Health and Health Disparities.



### **James Gordon Mainprize, PhD**

Research Associate  
Physical Sciences Platform, Sunnybrook Research Institute  
Toronto, ON, Canada

James Mainprize is a research associate in the Physical Sciences Platform at Sunnybrook Research Institute, Toronto, Canada. His areas of research include many aspects of breast cancer screening: prediction of masking risk in mammography, comparative microsimulation modelling for breast cancer screening, breast phantom development and radiation risk. He also works in developing tools for pathology / medical imaging correlation in breast and prostate, and for 3D skull modelling for surgical planning. He has patents in detectors for mammography, masking risk, and craniofacial implant tools. He is a founding partner of Calavera Surgical Design, a custom craniofacial implant design company.



### **Yiqiu "Artie" Shen, PhD**

Assistant Professor, NYU Grossman School of Medicine

Dr. Yiqiu Shen is an Assistant Professor of Radiology at NYU Grossman School of Medicine. His research focuses on developing interpretable and data-efficient deep learning systems to process multi-modal clinical data. His work has been applied to a wide range of clinical areas, including breast cancer diagnosis using mammography and ultrasound, COVID-19 prognosis using chest X-rays, classification of lung cancer metastasis with histopathology images, and diagnosis of osteoarthritis from knee radiographs. Dr. Shen earned his Ph.D. in Data Science from New York University in 2023. Prior to his doctoral studies, he worked at Two Sigma Investments from 2014 to 2016. He received his B.S. degree in Computer Science from Rice University in 2010.



### **Rebecca Hubbard, PhD**

Professor of Biostatistics and Data Science, Brown University School of Public Health

Rebecca Hubbard is the Carl Kawaja and Wendy Holcombe Professor of Public Health and Professor of Biostatistics and Data Science at the Brown University School of Public Health. Her research focuses on development and application of statistical methodology for studies using data from electronic health records (EHR) and medical claims. This work encompasses evaluation of screening and diagnostic tests, clinical risk prediction, algorithmic fairness, and health services research. Dr. Hubbard's methodological research emphasizes development and deployment of statistical tools to support valid inference for EHR-based analyses, accounting for complex data availability and data quality issues, with a focus on application to studies of cancer screening and survivorship. She is an elected Fellow of the American Statistical Association, Co-Editor of the journal Biostatistics, and a statistical editor for the New England Journal of Medicine.



### **Anne Marie McCarthy, ScM PhD**

Assistant Professor of Epidemiology  
Division of Biostatistics, Epidemiology and Informatics  
University of Pennsylvania Perelman School of Medicine  
Philadelphia, PA

Dr. McCarthy is a Cancer Epidemiologist and Assistant Professor of Epidemiology in the Department of Biostatistics, Epidemiology and Informatics at the University of Pennsylvania Perelman School of Medicine. Dr. McCarthy received her doctoral training at Johns Hopkins Bloomberg School of Public Health, and completed a post-doctoral fellowship at Massachusetts General Hospital and Harvard Medical School. The goal of Dr. McCarthy's research is to reduce the burden of cancer through improved prevention and screening strategies, particularly for racial/ethnic minorities. Dr. McCarthy's current work is focused on implementing precision medicine approaches to breast cancer prevention and early detection. Specifically, her work aims to utilize novel breast imaging biomarkers and genetics to improve breast cancer risk assessment, with a focus on improving risk assessment for Black women.

**Hideko Yamauchi**

affiliation

bio

**Teruo Yamauchi**

affiliation

bio

**Joanne Hayashi**

affiliation

bio

**Add Bios**

## Faculty Disclosures

### Carla H. van Gils

I am principal investigator of the DENSE trial that has been funded by governmental, charity and commercial funders (Volpara, Bayer Pharmaceuticals).

I am principal investigator of the DENSE-2 trial that is being funded by ZonMW (Dutch governmental funding organization), Hologic, Siemens and Bayer.

Besides my position as a Professor of Clinical Epidemiology at the University Medical Center Utrecht, I have a position as Director of Dutch Cancer Society.

### James Gordon Mainprize

Financial/Collaborative Disclosures

I work in a lab that has research agreement with GE HealthCare on various topics in digital mammography and tomosynthesis

I am founder and partner of Calavera Surgical Design Inc, a craniofacial surgical design company.

Membership/Associations:

I am a member of the AAPM (Chair of the X-ray Breast Imaging Subcommittee) and ACR (member of the Screening Leaders Group)

I am licensed engineer by the Professional Engineers of Ontario

### Anne Marie McCarthy

My spouse is invested in Novilla Pharmaceuticals. This is unrelated to anything I will discuss.

## SMARTER BREAST AI

# ProFound Breast Health Suite



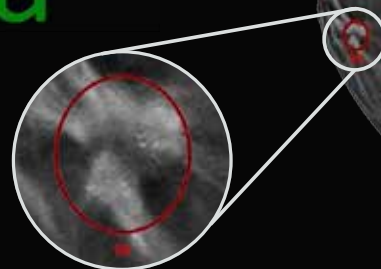
**Cancer  
Detection**



**Density  
Assessment**



**Risk  
Evaluation**



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# YOUR VOICE IS KEY TO CHANGING LIVES FOREVER.

The American Cancer Society is partnering with Black women to better understand why and how cancer and other health conditions disproportionately impact Black women in the US. Our groundbreaking VOICES of Black Women initiative is more than just a study; it's a collective commitment to understanding and improving the health of Black women across the nation – for generations to come.

With more than 70 years of trusted cancer research studies and breakthroughs under our belt, the American Cancer Society is uniquely positioned to make monumental change by identifying the root causes of health disparities among Black women and addressing those issues.

## WE NEED YOUR VOICE.

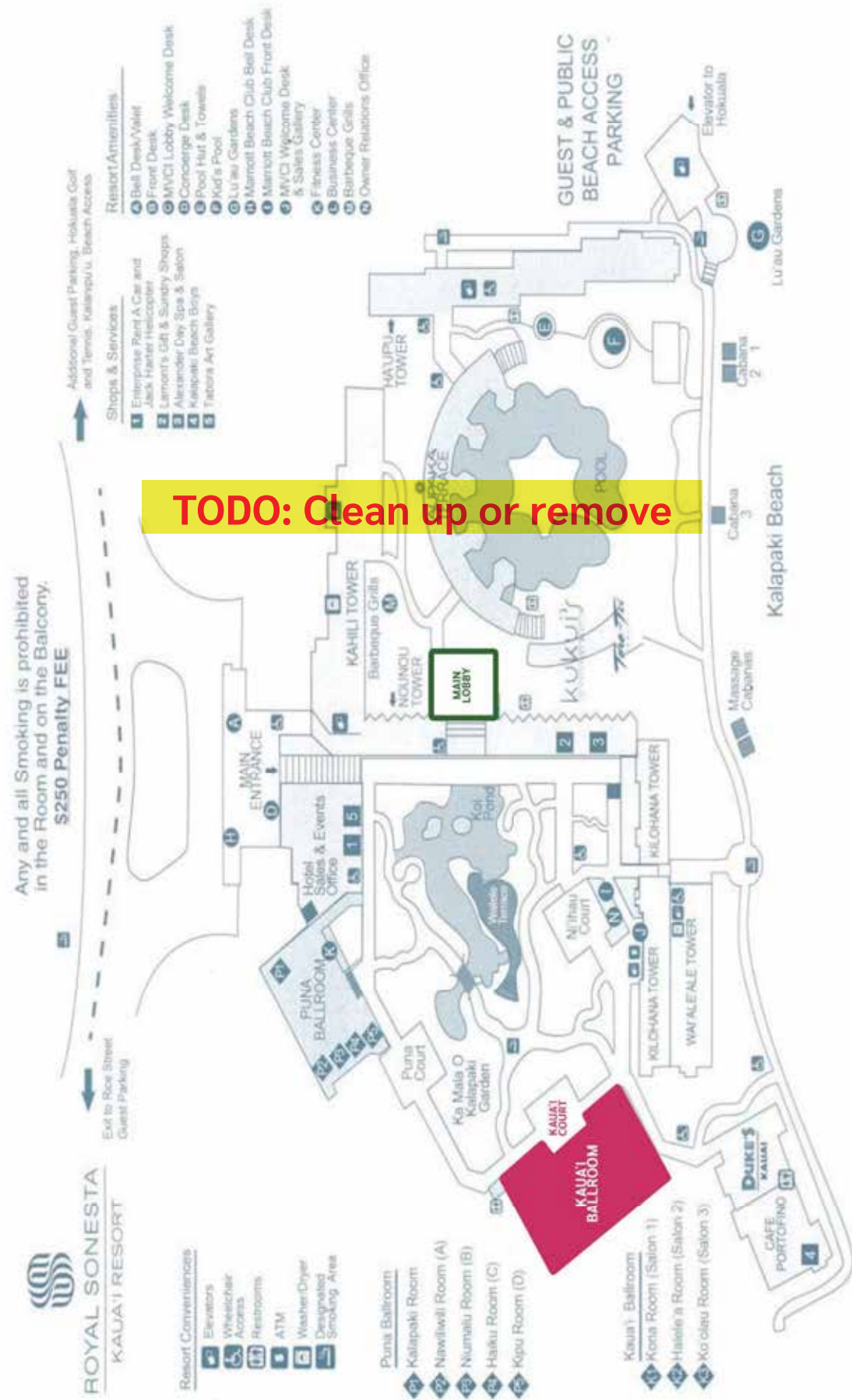
We are calling on Black women ages 25–55 who have never been diagnosed with cancer to join this movement. The time is now to help us change the future of cancer as we know it.

Visit [voices.cancer.org](https://voices.cancer.org) to learn more.

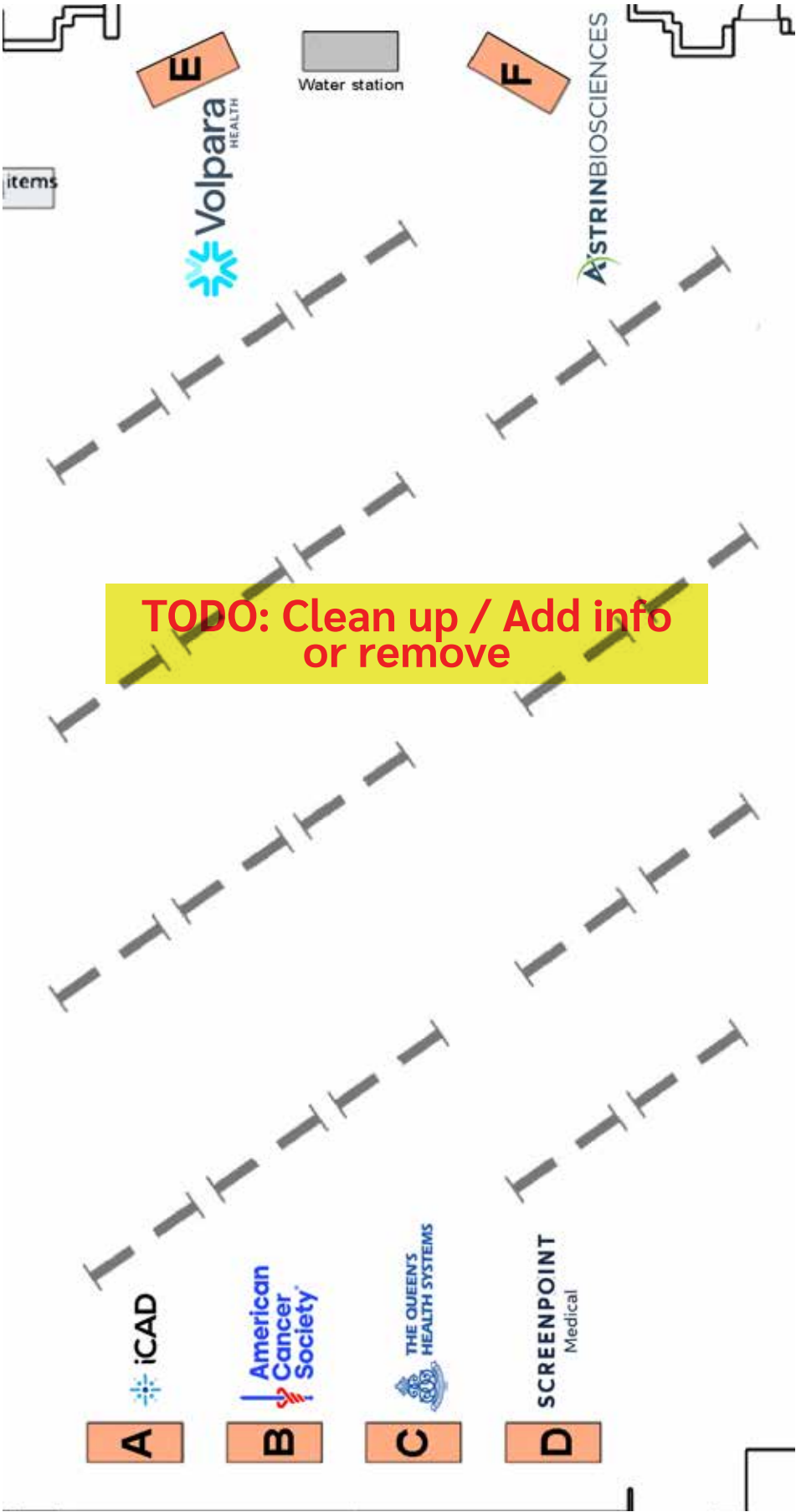


**VOICES**  
OF BLACK WOMEN





Map of Exhibitor Hall and Poster Sessions



## Registration

6:30 AM - 7:30 AM - - - - - Courtyard

## Breakfast

6:30 AM - 7:30 AM - - - - - Ko'olau + Halele'a Salon (2+3)

Sponsored by Volpara Health

## Welcome

7:30 AM - 8:20 AM - - - - - Kona Salon (1)

### Opening Oli Chant

Kahu Chucky Boy Chock

### Introduction

John Shepherd, PhD, University of Hawaii Cancer Center

Karla Kerlikowske, PhD, University of California San Francisco

### ADVOCATE

### Perspective from a Patient Advocate & Breast Cancer Survivor in Hawai'i

Joanne Hayashi, Breast Cancer Hawai'i

## State of the Art in Risk Assessment and Imaging Biomarkers

Moderator: Johnn Shepherd

8:20 AM - 9:45 AM - - - - - Kona Salon (1)

### PLENARY TALK

### Supplemental screening with MRI in women with extremely dense breasts: follow-up after three screening rounds of the randomized DENSE trial

Carla H. van Gils

Professor of Clinical Epidemiology of Cancer

Julius Center for Health Sciences and Primary Care

University Medical Center Utrecht

### ABSTRACT PROFFERED TALK - POSTER #74

### Association of genetic predisposition genes with breast density and breast cancer risk

Nicholas Boddicker, Mayo Clinic

### ABSTRACT PROFFERED TALK - POSTER #26

### Diagnostic accuracy of abbreviated magnetic resonance imaging for breast cancer screening among women with extremely dense breasts: a multi-reader study

Sophie van Grinsven, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University

## Coffee Break

9:45 AM - 10:15 AM - - - - - Ko'olau + Halele'a Salon (2+3)

## State of the Art in Risk Assessment and Imaging Biomarkers (Continued)

Moderator: John Shepherd

10:15 AM - 12:00 PM - - - - - Kona Salon (1)

### PLENARY TALK

### Mammographic Breast Density as a Predictive Biomarker among Women Diagnosed with Breast Cancer

Gretchen L. Gierach

Director and Senior Investigator, Integrative Tumor Epidemiology Branch

Division of Cancer Epidemiology and Genetics

National Cancer Institute

### ABSTRACT PROFFERED TALK - POSTER #19

### Population distribution of invasive and advanced breast cancer risk by breast density

Karla Kerlikowske, University of California San Francisco

### ABSTRACT PROFFERED TALK - POSTER #57

### Racial Differences in Background Parenchymal Enhancement, a Novel Marker for Breast Cancer Risk

Mattia Mahmoud, Perelman School of Medicine at the University of Pennsylvania

## Lunch

12:00 PM - 1:00 PM - - - - - Ko'olau + Halele'a Salon (2+3)

Before written language, Hawaiians devised the oli, elaborate chants, composed to record important information, e.g. births, deaths, triumphs, losses, good times and bad. Within the overall category of oli there are 1) genealogies, 2) tales of powerful chiefs, 3) stories of the beauty of various lands, and 4) expressions of love to woo a potential lover. A chanter oftentimes weaves kaona or double-meaning creating three, four, or five different levels of possible translation. So while some may hear the mele and think it means one thing, others more familiar with the context would understand a very different interpretation. It is often said that it is nearly impossible to fully understand the meaning of a chant because of this use of kaona. Only the intended recipient of the composition would be able to grasp its true meaning.

Kahu Chock will begin with a *kepakepa* style—a quick-paced chant—for the *Oli Kāhea*, asking permission to enter. He will then do the *Kaua'i Oli Ha'akulou*, a sacred chant specific to this island.



**Kahu Chucky Boy Chock**

Chucky Boy Chock is the Executive Director of the Kaua'i Museum, as well as a musician, composer, and minister. Originally from Kāne'ohe, O'ahu, he has lived on Kaua'i for 30 years and has devoted his life to building community and sharing the stories of the islands. In 2024, he was awarded the Keoki's Paradise Ho'oulu Award for his dedication to perpetuating Hawaiian history, culture, and traditions through storytelling and education centered on Kaua'i and Ni'ihau.

Chock became the director of the Kaua'i Museum on January 1, 2016 and before that had worked as a volunteer in charge of Events and Fundraising for 10 years. Established in 1960, the museum has become a vital resource for showcasing the rich history and artifacts of Kaua'i and Ni'ihau, with a particular focus on the legacy of King Kaumuali'i, the last independent ruler of the islands. Under Chock's leadership, the museum has expanded its exhibits and now also offers cultural workshops, serving as a bridge between the past and present for both locals and visitors.

Music is an essential part of Chock's story, with him starting out at the Kaua'i Museum by sharing his music and stories during special events. His passion for storytelling extends beyond the museum through his work as a musician and composer, using his art to foster connections and preserve cultural traditions. He is also actively involved in organizations that promote Hawaiian culture and music, including Kamawaelualani, the Hawai'i Association of Musicians, the Royal Order of Kamehameha (Kaumuali'i Chapter), the Polynesian Voyaging Society, and the Hawai'i Academy of Recording Arts.

**Supplemental screening with MRI in women with extremely dense breasts: follow-up after three screening rounds of the randomized DENSE trial**

CH van Gils<sup>1</sup> for the DENSE trial study group

1. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Over the past decade, numerous studies have investigated supplemental screening in women with dense breasts. While randomized controlled trials (RCTs) with breast cancer mortality as an endpoint are ideal, they require very large study populations and long follow-up periods. As an alternative, interval cancer and advanced cancer rates have been used as proxy outcomes, though such trials remain rare.

In 2019, we published initial results from the DENSE trial, an RCT evaluating supplemental MRI screening for women aged 50–75 with extremely dense breast tissue and normal mammography results. Participants were randomized into two groups: one invited for MRI (n=8061) and another receiving only standard mammography (n=32,312). Interval cancer rates were significantly lower in the MRI group (2.5 per 1000 screenings) compared to the mammography-only group (5.0 per 1000 screenings), ( $P<0.001$ ). Among the MRI-invited group, 59% accepted the invitation. Of the 20 interval cancers detected in this group, 4 occurred in those who underwent MRI (0.8 per 1000 screenings), while 16 were in those who declined MRI (4.9 per 1000 screenings). The cancer detection rate for women screened with MRI was 16.5 per 1000 screenings (95% CI, 13.3–20.5). The false-positive rate was 79.8 per 1000 screenings.

Women were eligible for a second round of MRI if their mammogram remained negative two years after their first MRI. The incremental cancer detection rate in the second round was 5.8 per 1000 screenings, compared to 16.5 per 1000 in the first round, alongside a significant reduction in false-positive rates (26.3 vs. 79.8 per 1000 screenings). Cost-effectiveness analyses using simulation models (MISCAN) confirmed the viability of MRI screening strategies.

**Key findings since 2023:**

The DENSE trial consisted of three rounds. The willingness to re-attend MRI screening was high, with re-attendance rates exceeding 80% in the second and third rounds. Meanwhile, follow-up information up to two years after the third screening round has been collected. In the presentation, I will share results on interval cancer rates after the second and third rounds, as well as advanced breast cancer rates during follow-up.

**Impact on screening strategies:**

Supplemental screening with MRI enables earlier detection of breast cancer in women with extremely dense breasts and allows for cost-effective screening strategies. It is, however, still costly and demands significant MRI and staffing capacity. The recently started DENSE-2 RCT evaluates contrast-enhanced mammography and abbreviated MRI as cheaper and more scalable options.

**Acknowledgements:** to trial participants, Dutch screening organization, Volpara Solutions, the Dutch Expert Centre for Screening, the National Institute for Public Health and the Environment, and the Netherlands Comprehensive Cancer Organization. The DENSE trial has been financially supported by the University Medical Center Utrecht, the Netherlands Organization for Health Research and Development, the Dutch Cancer Society, Pink Ribbon/a Sister's hope, Bayer AG Pharmaceuticals, and Stichting Kankerpreventie Midden-West.

(1) Bakker MF, de Lange SV, et al. Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. *N Engl J Med*. 2019;381:2091-2102.

(2) Veenhuizen SGA et al. Supplemental Breast MRI for Women with Extremely Dense Breasts: Results of the Second Screening Round of the DENSE Trial. *Radiology*. 2021;299(2):278-286.

(3) Geuzinge HA et al. Cost-Effectiveness of Magnetic Resonance Imaging Screening for Women With Extremely Dense Breast Tissue. *J Natl Cancer Inst*. 2021;113(11):1476-1483.

(4) Veenhuizen SGA, van Grinsven SEL et al. Re-attendance in supplemental breast MRI screening rounds of the DENSE trial for women with extremely dense breasts. *Eur Radiol*. 2024;34(10):6334-6347

## Mammographic Breast Density as a Predictive Biomarker among Women Diagnosed with Breast Cancer

GL Gierach<sup>1</sup>, C Bodelon<sup>2</sup>, M Mullooly<sup>3</sup>, C Ramin<sup>4</sup>, S Nyante<sup>5</sup>, S Fan<sup>1</sup>, A Hurson<sup>1</sup>, RM Pfeiffer<sup>1</sup>, EJ Aiello Bowles<sup>6</sup>, RE Curtis<sup>1</sup>, LHS Veiga<sup>1</sup>, H Spencer Feigelson<sup>7</sup>, L White<sup>7</sup>, S Weinmann<sup>8</sup>, JB Vo<sup>1</sup>, A Berrington de Gonzalez<sup>9</sup>, M Abubakar<sup>1</sup>

1. National Cancer Institute, Bethesda, MD, USA 2. American Cancer Society, Atlanta, GA, USA 3. RCSI University of Medicine and Health Sciences, Dublin, Ireland 4. Cedars Sinai Medical Center, Los Angeles, CA, USA 5. University of North Carolina, Chapel Hill, NC, USA 6. Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA 7. Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA 8. Kaiser Permanente Center for Health Research, Portland, OR, USA 9. Institute of Cancer Research, London, UK

**Introduction and objectives:** Elevated mammographic breast density (MBD) has been established as a strong, independent breast cancer risk factor. With increasing public awareness and accessibility to MBD measures in the clinic, there is an urgent need to better understand relationships between MBD and outcomes in women with breast cancer. **Methods:** In the Kaiser Permanente Breast Cancer Survivors Cohort, we retrieved archival serial mammograms along with tumor tissues to evaluate the role of temporal %MBD decline (using Cumulus) in relation to risk of: 1) breast cancer-specific death (n=97), among patients diagnosed with ER+ breast cancer and treated with tamoxifen (1990-2008, followed through 2010);<sup>1,2</sup> and 2) contralateral breast cancer (CBC, n=304), nested in a cohort of breast cancer survivors (n=10,734, diagnosed from 1990-2016, followed through 2017).<sup>3</sup> **Results:** 1) Among ER+ breast cancer patients, those who experienced MBD declines  $\geq 10\%$  vs  $< 10\%$  ~one-year post-tamoxifen initiation experienced reduced risk of breast cancer death (odds ratio [OR]=0.38, 95% confidence interval [CI]: 0.15-0.92).<sup>1</sup> To understand mechanisms underlying the prognostic value of MBD decline, we evaluated relationships with tumor molecular (luminal B-like vs A-like) and stromal characteristics. Machine-learning algorithms were used to characterize changes in stromal architecture and cell composition, i.e., stromal disruption, that are reminiscent of chronic inflammation and wound response on diagnostic H&E-stained images. The prognostic value of MBD decline was most apparent in patients with more aggressive ER+ phenotypes (i.e., luminal B-like).<sup>2</sup> The degree of MBD decline one-year post-tamoxifen initiation differed by extent of stromal disruption: luminal B-like patients with minimal stromal disruption experienced a mean 12.2% MBD reduction as compared with luminal B-like patients with substantial stromal disruption, who experienced a mean 3.8% MBD reduction. 2) Among breast cancer survivors, elevated %MBD both pre- (median=0.7 months before primary breast cancer) and post-diagnosis (median=11.6 months) was associated with  $\geq 2$ -fold increased risk of developing CBC, particularly of higher stage (II-IV) and grade (3/4). Furthermore, among ER+ breast cancer survivors treated with tamoxifen, a decline in %MBD of  $\geq 5\%$  from baseline to follow-up was associated with reduced CBC risk (OR=0.45, 95%CI: 0.22-0.93). **Conclusion:** MBD may serve as a predictive biomarker among women diagnosed with breast cancer. **Key finding:** Among ER+ breast cancer patients taking tamoxifen, MBD declines were associated with reduced risk of CBC and breast cancer death. **Impact on screening strategies:** Findings underscore the importance of surveillance among breast cancer survivors to monitor temporal changes in breast imaging features, ultimately informing clinical decision-making and improving breast cancer outcomes.

**Acknowledgements:** This work was supported in part by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

(1) Nyante SJ, Sherman ME, Pfeiffer RM, Berrington de Gonzalez A, Brinton LA, Aiello Bowles EJ, Hoover RN, Glass A, Gierach GL. Prognostic significance of mammographic density change after initiation of tamoxifen therapy for ER-positive breast cancer. *J Natl Cancer Inst* 2015;107. PMID: PMC4334825.

(2) Abubakar A, Mullooly M, Nyante S, Pfeiffer RM, Aiello Bowles EJ, Cora R, Bodelon C, Butler E, Butcher D, Sternberg L, Troester M, Weinmann S, Hoover RN, Sherman ME, Glass AG, Berrington de Gonzalez A, Gierach GL. Mammographic density decline, tamoxifen response, and prognosis by molecular characteristics of estrogen receptor-positive breast cancer. *JNCI Cancer Spectrum* 2022;6:pkac028. PMID: PMC9070642.

## Breakfast

7:00 AM - 8:00 AM - - - - - Ko'olau + Halele'a Salon (2+3)

Sponsored by Volpara Health.

## Housekeeping

8:00 AM - 8:10 AM - - - - - Kona Salon (1)

## Exploring the Biology and Modulators of Breast Density including Hormones, Obesity, and Environment

Moderator: Kimberly Bertrand

8:10 AM - 9:40 AM - - - - - Kona Salon (1)

### PLENARY TALK

#### National mammographic breast cancer screening in Korea and research based on the data: Risk Factors and Mortality Among Women With Interval Breast Cancer

Professor Boyoung Park, M.D., PhD.

Department of Preventive Medicine, Hanyang University College of Medicine

### PLENARY TALK

#### Why breast density can help us understand the role of environmental chemicals and breast cancer risk

Mary Beth Terry

Executive Director, Silent Spring Institute

Associate Director, Herbert Irving Comprehensive Cancer Center

Professor, Department of Epidemiology (Env Health)

Mailman School of Public Health

Columbia University Irving Medical Center

## Coffee Break

9:40 AM - 10:10 AM - - - - - Ko'olau + Halele'a Salon (2+3)

## Exploring the Biology and Modulators of Breast Density (Continued)

Moderator: Kimberly Bertrand

10:10 AM - 10:50 AM - - - - - Kona Salon (1)

### ABSTRACT PROFFERED TALK - POSTER #24

#### Body Fat, inflammation, and physical activity: insights into breast tissue composition in adolescent girls

Rebecca Kehm, Columbia University

### ABSTRACT PROFFERED TALK - POSTER #32

#### Investigating the impact of radiotherapy and endocrine therapy on mammographic breast density changes in the contralateral breast of breast cancer survivors

Amber Hurson, National Cancer Institute

## Breast Cancer Risk Board

Moderator: Fredrik Strand

10:50 AM - 12:00 PM - - - - - Kona Salon (1)

### PANEL

#### Breast Cancer Risk Board: An Open Discussion of Cases in the Style of a Tumor Board

Hideko Yamauchi, MD, The Queen's Health Systems

Teruo Yamauchi, MD, The Queen's Health Systems

Joanne Hayashi, Breast Cancer Hawai'i

Masako Kataoka, MD, Kyoto University

## Lunch

12:00 PM - 1:00 PM - - - - - Ko'olau + Halele'a Salon (2+3)

## Innovative Technology and Methods for Imaging Risk Assessment

1:00 PM - 2:00 PM

Moderator: Fredrik Strand

Kona Salon (1)

### PLENARY TALK

#### Mammatus: A Masking Risk Prediction Tool for Mammography

James Gordon Mainprize

Research Associate

Physical Sciences Platform, Sunnybrook Research Institute

Toronto, ON, Canada

### ABSTRACT PROFFERED TALK - POSTER #5

#### A 10-year breast cancer risk model based on image-data mediates modifiable risk factors targeted in primary prevention

Mikael Eriksson, Karolinska Institutet

## Poster Session 1

2:00 PM - 3:20 PM

Halele'a Salon (2)

ODD NUMBERS - View Poster Numbers and Abstracts on page 24

## Innovative Technology and Methods (Continued)

3:20 AM - 4:00 PM

Moderator: Fredrik Strand

Kona Salon (1)

### ABSTRACT PROFFERED TALK - POSTER #47

#### Assessing breast cancer risk using an AI model combining lesion detection and mammographic texture

Nico Karssemeijer, ScreenPoint Medical

### ABSTRACT PROFFERED TALK - POSTER #25

#### Improving Screening Performance by Ordering Mammogram Interpretation Batches Based on Breast Density

Jessie Gommers, Department of Medical Imaging, Radboud University Medical Center

# Smart AI for early breast cancer detection and diagnosis

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## National Mammographic Breast Cancer Screening in Korea and Research Based on the Data: Risk Factors and Mortality Among Women With Interval Breast Cancer

Boyoung Park<sup>1,2</sup>

1. Department of Preventive Medicine, Hanyang University College of Medicine, Republic of Korea 2. Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Republic of Korea.

**Introduction:** The Korean National Cancer Screening Program for breast cancer was launched in 2002 to provide biennial mammography for women aged  $\geq 40$  years for free of charge or at a co-payment of 10% of the total cost of the procedure depending on a participant's income status. The participation rate of national breast cancer screening has been increased; however, screening uptake rates still remain lower (38.4% in 2005 and 63.5% in 2020). Although mammographic breast cancer screening is effective in reducing breast cancer related mortality in women aged 40 to 74 years, there have been several issues related to mammographic screening such as overdiagnosis or interval breast cancer. **Objectives:** This study aimed to investigate differences between interval breast cancer (IBC) and screen-detected breast cancer (SBC) in Korean women, focusing on associated risk factors and mortality outcomes. **Methods:** Data from the National Health Insurance Service were used to analyze women who underwent nationwide mammographic screening between 2009 and 2012. IBC was defined as cancers diagnosed 6–24 months after a negative screening result, while SBC referred to cancers diagnosed within 6 months of a positive screening result. The mortality outcome was calculated from the date of breast cancer diagnosis to the date of death or 2020. In addition, established risk factors of breast cancer were compared between SBC and IBC. **Results:** Women with IBC were generally younger, had lower BMI, and more often used HRT after menopause compared to those with SBC. Additionally, increased mammographic density was inversely associated with IBC. Mortality risk analysis revealed that IBC had a higher risk of cancer-related deaths, particularly in those diagnosed within 6–12 months after negative screening. No significant differences in overall or cause-specific mortality were observed between IBC and SBC for longer diagnosis periods. **Conclusion:** Breast density is associated with IBC; additional research is warranted to determine whether a shortened screening period and new screening strategies are needed for women with risk factors for IBC. **Key finding:** Overall mortality of IBC was comparable with that of SBC. Higher supplemental breast ultrasound use among Korean women, especially those with dense breasts, could be attributed to a lower incidence of IBC among women with dense breasts compared with women with SBC, due to greater detection. **Impact on screening strategies:** The importance of investigating factors influencing IBC in Asian populations and potential improvements to breast cancer screening strategies for women to reduce missed cancers are suggested

(1) Choi E et al. Effectiveness of the Korean National Cancer Screening Program in reducing breast cancer mortality. *npj Breast Cancer*. 2021; 7:83.

(2) Song H et al. Risk Factors and Mortality Among Women With Interval Breast Cancer vs. Screen-Detected Breast Cancer. *JAMA Network Open*. 2024;7(5):e2411927

**Why breast density can help us understand the role of environmental chemicals and breast cancer risk**Mary Beth Terry<sup>1,2</sup>

1. Silent Spring Institute 2. Columbia University

**Introduction:** Most studies of environmental chemicals and breast cancer risk have been conducted without considering underlying susceptibility. In the studies that do consider susceptibility including enriched cohorts considering germline susceptibility and birth cohort studies considering windows of susceptibility (WOS), the epidemiological evidence between environmental chemicals and breast cancer risk is much more consistent. Given the long latency between exposures and cancer, intermediate markers are essential both to understand mechanisms across WOS as well as for intervention studies focused on reducing environmental exposures. Use of different methods to measure breast density may provide additional evidence linking environmental chemicals to breast cancer risk, as well as demonstrate the feasibility of breast tissue characteristics (BTC) to be used in future intervention studies.

**Objectives:** This talk will review the evidence to date supporting associations between environmental chemicals and breast density. We also will present new data from a mother-daughter cohort that measured chemicals during WOS and BTC as well as new data on untargeted high-resolution metabolomic profiling and BTC.

**Methods:** We conducted several studies examining targeted environmental chemicals during WOS and mammographic density as well as BTC including a prospective analysis using stored biospecimens from a New York City cohort of mother-daughter dyads. Exposure to 8 polycyclic aromatic hydrocarbons (PAH) were measured during the prenatal WOS (daughters) and pregnancy WOS (mothers) and third-trimester maternal urine samples were analyzed for nine phthalate metabolites, comprising 3 low molecular weight (LMW) and 6 high molecular weight (HMW) compounds. During longitudinal follow-up of mother-daughter pairs, we collected additional blood samples to measure untargeted metabolomics and BTC chromophores: water, lipid, collagen, optical index. Higher water, lower lipid and higher optical density are associated with higher mammographic density.

**Results:** The sum of 8 PAH compounds was associated with higher water content ( $\beta_{\text{daughters}} = 0.42$ , 95% CI = 0.15-0.68;  $\beta_{\text{mothers}} = 0.32$ , 95% CI = 0.05-0.61) and higher optical index ( $\beta_{\text{daughters}} = 0.38$ , 95% CI = 0.12-0.64;  $\beta_{\text{mothers}} = 0.38$ , 95% CI = 0.12-0.65) in those exposed to household tobacco smoke during pregnancy; no associations were found in non-smoking households (interaction p values < 0.05). HMW phthalate MEHP was positively associated with the higher water content and optical index ( $\beta_{\text{daughters}} = 0.17$ , 95% CI = 0.02, 0.32 and  $\beta = 0.19$ , 95% CI = 0.03, 0.34, respectively). Opposing effects were noted between HMW and LMW classes in their association with lower and higher lipid content, respectively. Of the 418 annotated metabolites, we observed 45 that were statistically significantly correlated with water content in the daughter's BTC and 62 that were statistically significantly correlated with the water content in the mother's BTC (12 of these were the same metabolites). In both mothers and daughters the number of metabolites were more than what would be expected by chance (n=21).

**Conclusion:** BTC are associated with environmental chemical exposures during two key WOS.

**Impact on screening strategies:** Growing evidence supports that environmental chemical exposures are associated with breast density as well as breast cancer. Informing individuals at the time of breast cancer screening about ways to reduce environmental exposures within an integrated risk assessment strategy could improve breast cancer risk reduction. As more data emerges on exposomics, it may also be possible to directly measure an individual's risk as well as conduct intervention studies to reduce risk through an integrated panel of genetics, density, and exposomics.

**Add info about this panel**

## Meet the Queen's Breast Surgical Oncology Physician Team



KATHLEEN MAH, MD



ASHLEY MARUMOTO, MD



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**Mammatus: A masking risk tool for digital mammography**

James G Mainprize<sup>1</sup>, Olivier Alonzo-Proulx<sup>1</sup>, Martin J Yaffe<sup>1,2</sup>

1. Physical Sciences Platform, Sunnybrook Research Institute 2. Department of Medical Biophysics, University of Toronto

**Introduction:** In addition to being a known breast cancer risk factor, breast density (BD) also limits the sensitivity of mammography and breast tomosynthesis. This occurs because the x-ray attenuation of normal parenchyma and cancer are very similar, which reduces the contrast of lesions with BD. The complexity of tissue structure in the background also reduces the conspicuity of small, early cancers. Both factors tend to reduce lesion detectability. We refer to these effects on reducing lesion detectability as “masking”. Using density and signal detectability maps derived from the mammogram, we have developed a masking risk prediction tool, Mammatus. Generally, masking risk increases with increasing BD and varying textural features. In our original retrospective study<sup>1</sup>, based on 147 screen-detected cancers and 47 non-screen detected (interval) cancers, Mammatus yielded a masking risk score that can discriminate between these two categories (i.e., predict cancer masking) with an AUC = 0.75 [0.67-0.82]. It was also demonstrated that Mammatus is a more efficient stratifier than density alone in a simulated stratified screening program<sup>2</sup>. For example, if supplemental screening is offered to all dense breasted women (BI-RADS C & D) this would require 43% of the women to have supplemental screening, while potentially catching 64% of interval cancers. Using Mammatus, at the same capture rate of 64% of interval cancers would require only 28% of women referred to supplemental screening.

**Objectives:** The development of Mammatus will be discussed. Current research activity includes refinement, validation and clinical translation to a contemporary cohort collected across several institutions. The federated approach we used with our collaborators for image collection and analysis will be detailed.

**Methods:** To mitigate data-sharing issues related to privacy and custodianship of data, the code was deployed as federated system, to collect and process mammograms locally at each site. De-identified masking data could then be accessed via a web-interface by collaborators and shared. A research version of Mammatus was provided to several European collaborators to evaluate Mammatus on study cohorts evaluating aspects of supplemental screening as well as breast-cancer risk-based screening.

**Results:** Lesion sizes at detection tended to be larger (>15 mm) for high masking risk ( $p=0.03$ ) mammograms<sup>3</sup>. Mammatus appears to be able to generalize to different screening strategies (e.g. European dual-reader) and outperforms volumetric BD as a masking risk predictor<sup>4</sup>. Preliminary results at our institution with a cohort of 23 non-screen and 117 screen-detected cancers yielded an AUC = 0.70. Expanded data including two additional cohorts will be available shortly.

**Key finding:** Since 2023, Mammatus has been tested on retrospective cohorts in Canada and Europe, and initial findings are consistent with the original performance.

**Impact on screening strategies:** Mammatus has the potential to be an efficient stratifier for supplemental screening, as compared to breast density. Future work will be the implementation of Mammatus in a prospective stratified screening study

**Acknowledgements** This project was conducted with the support of the Ontario Institute for Cancer Research through funding provided by the Government of Ontario.

1. Mainprize JG, Alonzo-Proulx O, Alshafeiy TI, Patrie JT, Harvey JA, Yaffe MJ. Prediction of Cancer Masking in Screening Mammography Using Density and Textural Features. *Acad Radiol*. Published online 2018;1-12. doi:10.1016/j.acra.2018.06.011
2. Alonzo-Proulx O, Mainprize JG, Harvey JA, Yaffe MJ. Investigating the feasibility of stratified breast cancer screening using a masking risk predictor. *Breast Cancer Res*. 2019;21(1). doi:10.1186/s13058-019-1179-z
3. Hickman S, Pantelidou M, Black R, et al. Masking Risk Index: an evaluation to guide supplemental imaging for breast screening. *Breast Cancer Res*. 2019;21((Suppl 1)):0096.
4. Verboom SD, Mainprize JG, Broeders M, Yaffe MJ, Sechopoulos I. Evaluating the Generalizability of a Mammographic Masking Prediction Model to the Dutch Breast Cancer Screening Program. *Eur J Radiol*.

## Breakfast

7:00 AM - 8:00 AM - - - - - Ko'olau + Halele'a Salon (2+3)

Sponsored by Volpara Health.

## Housekeeping

8:00 AM - 8:10 AM - - - - - Kona Salon (1)

## Frontiers in Breast Cancer Risk Assessment: Integrating Clinical, Omic, and Imaging Biomarkers

Moderator: Karla Kerlikowske

8:10 AM - 10:00 AM - - - - - Kona Salon (1)

### PLENARY TALK

**Advancing Breast Cancer Risk Prediction Through Deep Learning on Multimodal and Longitudinal Imaging Data**

Yiqiu "Artie" Shen

Assistant Professor

NYU Grossman School of Medicine

### ABSTRACT PROFFERED TALK - POSTER #33

**Improved Long-Term Breast Cancer Risk Prediction Through Analysis of Sequential Mammograms Leveraging State-of-the-art AI Model**

Juanita Hernandez, Washington University School of Medicine in St. Louis

### ABSTRACT PROFFERED TALK - POSTER #1

**Validated Dynamic Model Leveraging Prior Mammograms to Predict 5-Year Breast Cancer Risk**

Joy Jiang, Washington University

### ABSTRACT PROFFERED TALK - POSTER #48

**Performance of Clinical Breast Cancer Risk Prediction Models Versus a Mammography-Based AI Risk Model**

Medha Kaul, Mayo Clinic Rochester, Minnesota

## Coffee Break

10:00 AM - 10:30 AM - - - - - Ko'olau + Halele'a Salon (2+3)

## Frontiers in Breast Cancer Risk Assessment (Continued)

Moderator: Karla Kerlikowske

10:30 AM - 11:30 AM - - - - - Kona Salon (1)

### ABSTRACT PROFFERED TALK - POSTER #53

**Comparative 15-year Performance of Mammography Artificial Intelligence, Clinical Breast Cancer Risk, and Polygenic Risk Models at Kaiser Permanente Northern California**

Vignesh Arasu, Kaiser Permanente Division of Research

### ABSTRACT PROFFERED TALK - POSTER #77

**Racial/ethnic differences in the performance of radiomic and genomic breast cancer risk prediction models**

Weiva Sieh, MD Anderson Cancer Center

### ABSTRACT PROFFERED TALK - POSTER #66

**Mammography AI Models and Radiomic Features for 5-year Advanced-Stage Breast Cancer Risk Prediction: A Matched Case-Control Study in an Ethnically-Diverse Cohort**

Arianna Bunnell, University of Hawaii Cancer Center

## Lunch

11:30 AM - 12:30 PM - - - - - Ko'olau + Halele'a Salon (2+3)

## Engaging Communities to Improve Risk Models and Screening Strategies Toward Health Quality for All Women

12:30 PM - 1:50 PM

Moderator: Celine Vachon

Kona Salon (1)

### ADVOCATE - POSTER #30

**Communicating Breast Density and Breast Cancer Risk: Global Insights, Local Lessons, and the Consumer Voice**

Sandy Minck, Dr Sandy Minck

### PLENARY TALK

**Disaggregating Disparities in Surveillance Mammography Performance and Risk-Guided Surveillance Imaging Recommendations Using Synthetic Data**

Rebecca Hubbard

Professor of Biostatistics and Data Science, Brown University School of Public Health

### ABSTRACT PROFFERED TALK - POSTER #7

**The psychosocial and health service impact of breast density notification – findings from Australia's screening program-embedded randomised controlled trial**

Brooke Nickel, Baylor University Medical Center

## Poster Session 2

1:50 PM - 3:10 PM

Halele'a Salon (2)

**EVEN NUMBERS - View Poster Numbers and Abstracts on page 26**

## Engaging Communities (Continued)

3:10 PM - 4:15 PM

Moderator: Celine Vachon

Kona Salon (1)

### PLENARY TALK

**Impact of Breast Density on Racial Disparities in Breast Cancer**

Anne Marie McCarthy, ScM PhD

Assistant Professor of Epidemiology

Division of Biostatistics, Epidemiology and Informatics

University of Pennsylvania Perelman School of Medicine

Philadelphia, PA

### ABSTRACT PROFFERED TALK - POSTER #73

**Fairness In AI-Based Mammography Screening: A Multi-Region Preliminary Study**

Fredrik Strand, Karolinska Institutet

## New Frontiers in Breast Cancer Research and Management

5:00 PM - 7:00 PM

Open to the Public

Kona Salon (1)



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## Advancing Breast Cancer Risk Prediction Through Deep Learning on Multimodal and Longitudinal Imaging Data

Yiqiu Shen<sup>1</sup>, Yanqi Xu<sup>2</sup>, Jungkyu Park<sup>1</sup>, Felicia Pasadyn<sup>1</sup>, Laura Heacock<sup>1</sup>, Linda Moy<sup>1</sup>, Krzysztof J Geras<sup>1</sup>

1. NYU Grossman School of Medicine 2. NYU Center for Data Science

**Introduction:** Breast cancer risk stratification is critical for reducing the breast cancer burden. Current standard-of-care models, relying on coarse risk factors, often yield inadequate accuracy. **Objectives:** This project aims to improve the accuracy of breast cancer risk prediction using a deep learning (DL) model that integrates longitudinal and multimodal breast imaging (FFDM, DBT, and ultrasound). **Methods:** We trained our DL model, named Multi-modal Transformer (MMT), on the NYU Multimodal Breast Cancer Dataset, which includes 1.48 million FFDM, DBT, and ultrasound exams from 298,702 patients (mean age 54.47; 13,114 developed breast cancer within 5 years). Internal evaluation was conducted on the NYU Matched Case-Control Dataset (n=936), consisting of 468 patients who developed breast cancer within five years and 468 matched controls (matched by age, breast density, and race/ethnicity) who remained cancer-negative after imaging for at least 5 years. There was no patient overlap between the training and case-control datasets. External validation was performed on two datasets: the Emory dataset (25,980 FFDM and 2,528 ultrasound exams from 9,681 patients; mean age 59.8; 259 cancer-positive within 5 years) and the Polish Military Hospital (PMH) dataset (916 FFDM and 465 ultrasound exams from 454 patients; mean age 59.8; 6 cancer-positive within 2 years). To evaluate risk prediction rather than cancer detection, imaging exams with a cancer diagnosis within 120 days were excluded. Model performance was evaluated using 1–5-year concordance index (C-index). We compared our model's performance to MIRAI, a deep learning model based on static FFDM exams, and the standard-of-care Tyrer-Cuzick (T-C) model. Our DL model uses a transformer architecture to integrate visual features from current and up to three years of prior imaging exams to predict 1–5 year breast cancer risk. The architecture of MMT is illustrate in Figure 1. **Results:** On the NYU Matched Case-Control Dataset (n=936, 468 cancers), our model achieved a C-index of 0.758 (95% CI: 0.738–0.778), outperforming MIRAI (0.657, 95% CI: 0.632–0.681) and Tyrer-Cuzick (0.605, 95% CI: 0.579–0.632). On the Emory dataset, our model reached a C-index of 0.699 (95% CI: 0.668–0.730), compared to MIRAI (0.680 95% CI: 0.650–0.710) and Tyrer-Cuzick (0.462 95% CI: 0.440–0.488). On the PMH dataset, our model achieved a C-index of 0.857 (95% CI: 0.740–0.963), compared to MIRAI's 0.777 (95% CI: 0.592–0.947). **Conclusion:** Our results show that MMT outperforms the T-C model, confirming that breast imaging provides prognostic value beyond traditional clinical variables. MMT also consistently outperformed MIRAI, which relies solely on static FFDM images, supporting our core hypothesis that incorporating multimodal imaging—FFDM, DBT, and ultrasound—improves breast cancer risk prediction accuracy. **Key finding:** Longitudinal tissue changes observed in multimodal breast imaging provide valuable prognostic information that enhances breast cancer risk prediction. **Impact on screening strategies:** Image-based deep learning models improve breast cancer risk prediction. Accurate risk stratification has the potential to support selective use of supplemental modalities such as MRI, enable personalized screening strategies, and ultimately improve overall screening cost-effectiveness.

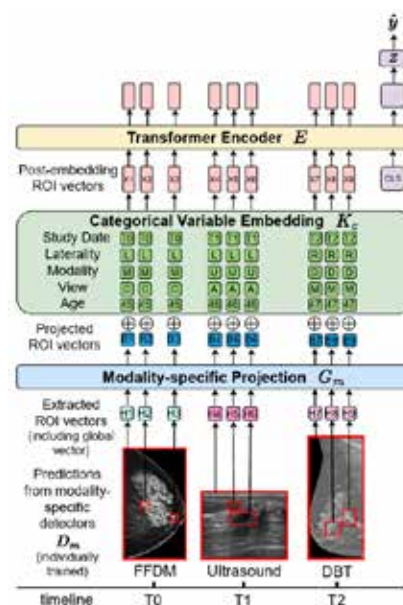


Figure 1: Architecture of MMT.

## Disaggregating Disparities in Surveillance Mammography Performance and Risk-Guided Surveillance Imaging Recommendations Using Synthetic Data

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**Introduction:** Annual surveillance mammography is recommended for all women with a history of breast cancer. Risk-guided surveillance incorporating advanced imaging modalities based on individual risk of a second cancer could improve cancer detection. However, personalized surveillance strategies risk exacerbating disparities in cancer outcomes due to the limited inclusion of minority racial and ethnic groups in risk model development data, heterogeneity in outcome ascertainment, and the influence of race and ethnicity on patient characteristics that influence cancer risk and mammography effectiveness. **Objectives:** This study seeks to disaggregate structural contributors to disparities in surveillance mammography performance and risk-guided imaging recommendations, specifically distinguishing between disparities driven by characteristics of the primary breast cancer and its treatment versus those stemming from social determinants of health (SDOH). **Methods:** Using synthetic cohorts based on data from the Breast Cancer Surveillance Consortium (BCSC), we explored disparities associated with race and ethnicity. We decomposed these disparities into components attributable to primary breast cancer and treatment factors, SDOH, and differential error in second cancer ascertainment. Synthetic cohorts were generated with or without variations in these factors across racial and ethnic groups. The resulting impacts on mammography performance and supplemental imaging recommendations were analyzed across racial and ethnic groups. **Results:** In synthetic cohorts derived from 65,446 BCSC surveillance mammograms, when differences across race and ethnicity groups were limited to cancer characteristics, mammography sensitivity was lower for Black women compared to the overall population (64.1% vs. 71.1%). The disparities widened when both cancer characteristics and SDOH varied by race and ethnicity (53.8% vs. 71.1%). Risk-based recommendations for supplemental imaging were less frequent for Hispanic (6.7%) and Asian/Pacific Islander women (6.4%) than for the overall population (10.0%). **Conclusions:** Disparities in surveillance mammography performance and risk-based recommendations for supplemental imaging were influenced by variations in cancer characteristics and SDOH. Key finding: Risk-guided surveillance could introduce disparities in recommendations for advanced imaging modalities, even when race and ethnicity are not included as explicit predictors in risk models. Impact on screening strategies: Decision-makers should consider cancer equity implications before implementing risk-based screening practices.

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**Impact of breast density on racial disparities in breast cancer**Anne Marie McCarthy<sup>1</sup>**1.** Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania

In the U.S., racial disparities in breast cancer mortality have persisted, with Black women experiencing 40% higher mortality than white women despite a lower breast cancer incidence. Black women are more likely to be diagnosed with advanced-stage breast cancer, even among women who undergo mammography screening. Interestingly, Black women have lower BI-RADS breast density (21% heterogeneously or extremely dense breasts) compared to white women (41%). However, this difference may reflect larger breast size and higher BMI among Black women. Our studies have shown that Black women have greater levels of dense breast tissue than white women when measured quantitatively and suggest that quantitative breast density measures, in particular dense volume from digital breast tomosynthesis, may provide a more accurate assessment of breast tissue among Black women. Despite differences in breast density levels by race, we found similar levels of background parenchymal enhancement (BPE) on breast MRI between Black and white women. BPE is associated with both with hormonal factors and breast cancer risk. This may indicate that Black women have similar levels of hormonally active tissue in the breast as white women, making BPE a potentially valuable risk marker. Breast density measurement has growing importance as evidence accumulates of the benefits of supplemental screening for women with dense breasts, and given expanding access to supplemental screening in the U.S. A growing number of states have laws that direct insurance coverage of supplemental screening using BI-RADS density, which results in few Black women qualifying for coverage. Use of quantitative measures, or consideration of density plus other risk factors such as BMI may better identify high-risk Black women who would benefit from supplemental screening. Supplemental screening remains underutilized, but particularly so among Black women. In our institution, 28% of women with extremely dense breasts had a supplemental screening ordered by their provider within six months, compared with 7% of Black women. We performed a randomized controlled trial of electronic health record nudges and found that text messaging patients and including recommendation for breast MRI screening in mammography reports significantly increased utilization and reduced racial disparities in supplemental screening for patients with extremely dense breasts. **Key finding:** Differences in breast density by race may impact breast cancer risk assessment and access to supplemental screening. **Impact on screening strategies:** Our recent work highlights the need to improve equitable implementation of both risk assessment and supplemental screening to avoid exacerbating disparities in breast cancer outcomes.

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Jennifer Stone, University of Western Australia
5. **A 10-year breast cancer risk model based on image-data mediates modifiable risk factors targeted in primary prevention**  
Mikael Eriksson, Karolinska Institutet
7. **The psychosocial and health service impact of breast density notification – findings from Australia's screening program-embedded randomised controlled trial**  
Brooke Nickel, Baylor University Medical Center
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Anna (Dulashi) Withanage Dona, The University of Melbourne
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## Validated Dynamic Model Leveraging Prior Mammograms to Predict 5-Year Breast Cancer Risk

Shu Jiang, PhD; Debbie L. Bennett, MD; Bernard A. Rosner, PhD; Rulla M. Tamimi, ScD; Graham A. Colditz, MD, DrPH

Current image-based long term risk prediction models do not fully utilize existing data. Dynamic risk prediction models that incorporate current and prior screening mammogram images have not been investigated for use in routine care.

The dynamic model was trained on a prospective WashU clinic-based cohort of 10,099 cancer-free women at cohort entry (recruited from women attending routine screening between Nov 3, 2008 and February 2012). Follow-up through 2020 identified 478 pathology-confirmed breast cancer cases. The cohort included 27% non-Hispanic Black women.

Two external validation cohorts were included in this study. The first is Emory cohort included 18,360 women screened from 2013 and followed through 2020. This included 42% non-Hispanic Black women and 332 pathology-confirmed breast cancer cases. The second is a prospective Cohort of 208,313 women 40 to 74 drawn from the British Columbia Cancer (BC Cancer) Breast Screening program screened from Jan 2013 to Dec 31, 2019. We identified 3,021 pathology-confirmed incident breast cancers diagnosed through June 20, 2023.

In the Emory cohort, using 3 years of prior mammogram images available at the current screening mammogram, after excluded cases diagnosed within 6 months of screening, we obtained a 5-year AUC of 0.80 (95% CI, 0.78, 0.83) when controlling for age and BI-RADS density. Evaluating model performance in the same women, this represents a significant improvement over only using the current visit mammogram AUC 0.74 (95% CI, 0.71, 0.77) ( $p < 0.01$ ). In the BC Cancer cohort, using up to 4 years of prior mammogram images in addition to the current mammogram, we obtained a 5-year AUC of 0.78 (95% CI, 0.76 – 0.80) based on analysis of images alone, again representing a significant gain comparing to using the current visit mammogram [AUC = 0.71 (95% CI, 0.69, 0.73)].

When calibrated to SEER 5-year incidence rates, a risk ratio of 21.1 was observed in the Emory Cohort comparing high (>4%) to very low (<0.3%) 5-year risk. Similarly, a risk ratio of 24.4 was observed in BC Cancer.

**Key Finding:** Adding previous screening mammogram images improves 5-year breast cancer risk prediction beyond static models.

**Impact on Screening Strategy:** It can identify women at high risk who might benefit from supplemental screening or risk reduction strategies.

**Beyond Breast Density: Generalizability of an AI-Based Mammogram Risk Score (MRS) Across Racially and Ethnically Diverse Women**

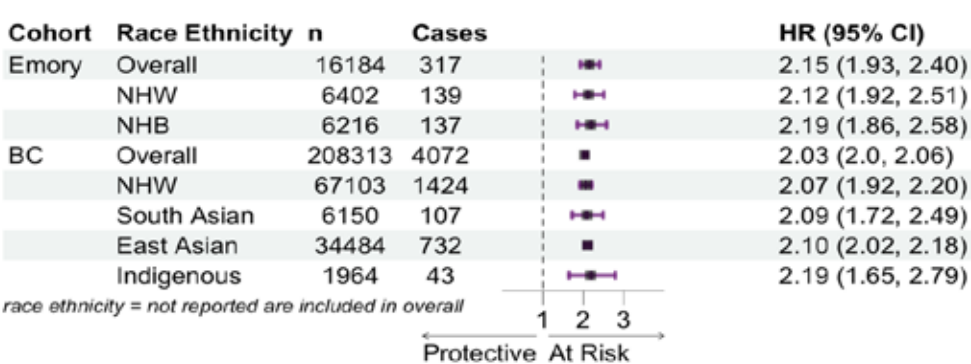
Graham A Colditz<sup>1</sup>, MD DrPH; Debbie L. Bennett<sup>1</sup>, MD; Peter Kraft<sup>2</sup>, PhD; Shu Jiang<sup>1</sup>, PhD

1.Washington University School of Medicine and 2.National Cancer Institute

**Introduction:** A major challenge in breast cancer risk prediction lies in accurately identifying women at elevated risk across diverse racial and ethnic groups. Mammogram risk scores (MRS), an AI-driven feature summarizing mammographic texture, have shown potential to accurately classify 5-year breast cancer risk in racially diverse populations<sup>1</sup>. We ask do they preform across race and ethnic groups to ensure the model’s generalizability?

**Methods:** To address this question, we analyzed data from two large North American cohorts—Emory and British Columbia—encompassing over 226,000 racially diverse women, including Non-Hispanic White (NHW), Non-Hispanic Black (NHB), East Asian, South Asian, and Indigenous women. We assessed the distribution of MRS by race and ethnicity and observed little variation in median MRS between the two cohorts overall, among race and ethnicity groups within each cohort, or between cohorts within race and ethnicity (where such comparisons were feasible).

**Results:** We further examined the association between MRS and breast cancer risk both overall and stratified by race/ethnicity. Increase in MRS was associated with breast cancer; the hazard ratios (HR) per standard deviation increase in MRS ranging from 2.03 (95% CI: 2.00–2.06) to 2.15 (95% CI: 1.93–2.40) after adjusting for age (Figure). This significant association was consistent across racial/ethnic groups: NHB (2.12, 95% CI: 1.92–2.51), East Asian (2.10, 95% CI: 2.02–2.18), South Asian (2.09, 95% CI: 1.72–2.49), and Indigenous women (2.19, 95% CI: 1.65–2.79). Prediction accuracy, as assessed using the 5-year AUC, also showed no statistically significant differences by race/ethnicity within each cohort.



**Conclusion:** The consistent association between the MRS and breast cancer across race and ethnic groups together with distribution of MRS across these groups supports the use of MRS as a summary of the breast issue composition that conveys the functional summary of the final common pathway underlying tissue to breast cancer.

**Key finding:** The lack of any clinically meaningful differences in MRS performance across a broad range of race and ethnic groups supports broad applicability.

**Impact on Screening Strategy:** The MRS could be effectively used in clinical practice to estimate age-specific breast cancer incidence, including for individuals with mixed ancestry or self-reported identities commonly encountered in real-world settings

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## The impact of breast density notification on interval cancer detection rates

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**Background:** Increased breast density is associated with increased breast cancer risk, particularly interval-detected cancers. Interval cancer detection rates typically increase with time from mammographic screening. The impact of breast density notification on interval cancer detection rates and timing of diagnoses is largely unknown. This study describes interval cancer detection rates for women who were notified they had dense breasts compared to those who were not flagged as having dense breasts, stratified by the period of follow-up since screening (0-12 months vs 13-24 months).

**Methods:** 300,787 screening records for 214,712 clients attending a population-based screening program in 2016-2019 were extracted from the BreastScreen Western Australia database. Crude and age-adjusted interval cancer rates, aggregated over three-year periods, were calculated per 10,000 client-years and reported by breast density notification status, screening round, and timing of diagnoses.

**Results:** Overall, interval cancer detection rates were 2-6 times higher in clients notified they had dense breasts compared to those who were not flagged as having dense breasts. The 2016-2018 estimated interval cancer detection rates after a normal screening mammogram were higher in the first year (vs second year) for clients notified they had dense breasts (27.8 vs 20.4 per 10,000 client-years, respectively), particularly notified clients screening for the first time (32.4 vs 18.6, respectively). There were negligible differences between the corresponding 2017-2019 estimated rates for notified clients (16.5 vs 15.2 for 0-12 vs 13-24 months, respectively), regardless of screening round.

**Conclusion:** Within women notified they had dense breasts, interval cancer rates were at least similar or higher in the first 12 months compared to 13-24 months post screening, contrary to national reports of interval cancer detection rates in Australia. Larger studies are needed, with individual-level data on the uptake of supplemental screening, to further assess the impact of breast density notification on interval cancer detection rates.

## **Refining tamoxifen dose for premenopausal breast cancer risk reduction (RENAISSANCE): A Phase II single-arm trial**

Khan SA, Kocherginsky M, Benante K, Xu Y, Schering T, Amin AL, Chow HHS, Fabian CJ, Hoskins K, Hughes KL, King TA, Pilewskie ML, Thomas P, Toriola A, Eriksson M, Krol D, Heckman-Stoddard B.

**Background:** The breast cancer prevention efficacy of tamoxifen 20 mg/day is proven, but acceptance by high-risk women remains low, including among premenopausal women, for whom tamoxifen is the only proven prevention option. Low-dose tamoxifen (5 mg/day) has demonstrated promising efficacy in postmenopausal, but not premenopausal women, for whom we are testing a novel personalized dosing strategy to define the lowest effective dose. Since breast density reduction is a promising surrogate for prevention efficacy, we will address the provocative question: can absolute dense area reduction (aDAR) on mammogram function as a surrogate for tamoxifen efficacy, allowing personalization of tamoxifen dose for premenopausal women?

**Methods:** Our single-arm Phase II trial is enrolling 200 high-risk premenopausal who are candidates for tamoxifen risk-reduction at 10 sites across the US. Exclusions: A prior history of invasive breast cancer, a history of tamoxifen use, or medical contraindications to tamoxifen. After a baseline mammogram, participants will start tamoxifen 5 mg/day, with repeat mammography 6 months later. We expect 30% to be non-responders (aDAR $\geq$ 10%). They will be escalated to 10 mg/d, and those whose aDAR remains under 10% at 12 months will be advised to escalate to 20 mg/d. Quantitative density measurement will be performed using the Karolinska STRATUS algorithm. Blood samples for secondary endpoints will be obtained at 6, 12, 18, months. A core needle breast biopsy will be conducted for research prior to TAM initiation and at the end of the first 6 months of use.

**Expected results:** We estimate that the total proportion of premenopausal tamoxifen responders can be increased by 10% through dose escalation from 5 mg to 10 mg/day, using mammographic aDAR as an indicator of tamoxifen response (82% power to detect an increase in total responder fraction from 70% to 80% at 12 months). Additionally, breast density may decrease further with longer use; patient-reported symptoms will be less severe at lower doses; adherence to TAM use will be higher. We will also explore breast density reduction correlation with plasma levels of endoxifen, gene polymorphisms influencing breast density and TAM metabolism, and breast cancer risk estimates derived from artificial intelligence algorithms.

**Conclusions:** This will be the first trial in the cancer prevention arena to test the hypothesis that the dose of a risk-reducing medication can be optimized using a surrogate measure of efficacy. If successful, it will advance the cause of using the "minimal effective dose" for cancer prevention.

**Key Finding:** Enrollment has been brisk, and premenopausal women are open to a strategy of dose escalation if guided by an objective measure of tamoxifen response. **Impact on Screening Strategies:** No direct impact on screening; main impact of our trial will be in the form of increased acceptance of preventive medication.

## **A 10-year breast cancer risk model based on image-data mediates modifiable risk factors targeted in primary prevention**

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**Background:** Image-derived AI-based risk models have demonstrated the ability to identify up to 40% of breast cancers (BC) as high-risk within a 10-year follow-up period. However, the extent to which modifiable BC risk factors are explained by such AI-derived risk scores remains unknown.

**Methods:** We conducted a case-cohort study involving women aged 40-74 recruited between 2010 and 2016 from the Swedish KARMA screening cohort, with a median follow-up of 10 years. Breast cancers diagnosed by June 2022 were included. The AI risk tool estimated absolute 10-year BC risk at study entry. Causal mediation analyses estimated mediation effects of lifestyle factors, breast density (BD), benign breast disease (BBD), and family history (FH) to BC risk using the AI score as a mediator. Hazard ratios (HRs) and percentages of mediation were reported overall and for subgroups stratified by menopause status and follow-up time.

**Results:** The study included 2,985 women in the subcohort (mean age 54.4 years, SD  $\pm$  9.7) and 500 incident BC cases (mean age 57.5 years, SD  $\pm$  9.4). In postmenopausal women, the AI score significantly mediated BC risk of weight (58.1%), BD (36.1%), BBD (31.8%), and FH (23.8%). In premenopausal women, BD (26.8%), BBD (36.1%), and FH (18.9%) were significantly mediated. These mediation effects varied with follow-up duration.

**Key Findings:** The image-derived AI-based risk model mediated established BC risk factors, including weight, BD, and BBD that are causal of breast cancer. Primary prevention strategies may benefit from selecting women using an AI-based risk tool to perform interventions that modifies weight, breast density, and intercept BBD progressing into breast cancer.

**Impact on Screening Strategies:** An AI-based primary prevention risk model based on image data could be integrated into existing early detection infrastructure in an expanded joint early-detection—primary prevention screening program. Women at high 10-year risk of breast cancer may be offered a risk reducing lifestyle/medical intervention as a service in addition to the early detection of breast cancer.

Can Clustering of Deep Image Representations Reveal Latent Breast Cancer Risk Subtypes in a Multiethnic Population?

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**Introduction:** Deep learning (DL) has shown strong potential to uncover hidden representations predictive of breast cancer (BC) risk from mammographic images. Models like Mirai have outperformed traditional risk models such as Tyrer-Cuzick across diverse populations, but their “black-box” nature limits explainability and clinical trust [1, 2]. Enhancing interpretability is critical for clinical adoption, especially in personalized screening and risk-based prevention. One avenue for improving explainability is unsupervised clustering of learned image features. Clustering is a foundational tool in data-driven healthcare and bioinformatics, used to identify natural subgroups in complex, high-dimensional data [3]. It has been applied for risk stratification of patients using electronic health record (EHR) data with joint optimization of representation learning and subgroup discovery [4], as well as to analyze radiomic features of mammographic parenchymal complexity and their associations with BC risk factors such as age, BMI, and breast density [5]. While Gu et al. applied k-means clustering to risk factors identified through Cox regression models, followed by Kaplan–Meier survival curves to characterize breast cancer risk subtypes [6], to our knowledge, no study has applied unsupervised clustering directly to the latent features extracted from a DL-based survival model such as Mirai. This represents a novel opportunity to uncover clinically meaningful imaging-derived subgroups that reflect patterns learned by state-of-the-art risk models. **Objectives:** This aims to cluster the latent features extracted from the MIRAI breast cancer risk prediction model [1] to identify subgroups of women with distinct imaging phenotypes. These clusters will be evaluated for alignment with known breast cancer risk factors, such as breast density, BMI, and 5-year risk estimates [7], and explored for their potential to improve understanding of learned imaging-derived risk patterns. **Methods:** Participants were drawn from the Hawai'i and Pacific Islands Mammography Registry (HIPIMR; NIH R01CA263491 and U54CA143728), which includes over 125,000 women. We selected women aged 40–79 with negative diagnostic or screening mammograms with all four standard views and known breast density. Cases were those who developed invasive BC at least six months post-imaging, and matched controls were selected based on birth year, race/ethnicity, and imaging equipment. **Preliminary Results:** After excluding low-quality images, the final cohort comprised 3,776 controls and 1,307 cases. Using the pretrained Mirai model, we will extract 512-dimensional deep image representations and apply k-means clustering. We will use appropriate statistical tests to evaluate cluster associations with clinical variables such as BMI, breast density, and 5-year risk estimates (e.g., Kruskal–Wallis, chi-squared). Kaplan–Meier analysis and Cox regression will be conducted to evaluate survival patterns across clusters. **Key finding:** We anticipate that clustering deep learning-derived image features will reveal latent imaging phenotypes associated with distinct risk trajectories for invasive breast cancer. These clusters are expected to differ across key clinical factors, particularly those relevant to Hawai'i's multiethnic population, such as race/ethnicity, breast density, BMI, and age. We expect survival analysis to show that particular clusters are enriched for elevated or suppressed long-term risk, which may vary by ancestry and clinical characteristics. **Impact on screening strategies:** Clustering DL-derived mammography features may enhance the interpretability of risk models and support a new paradigm for imaging-based phenotyping. This could improve equity in risk stratification, ensuring that high-risk individuals are appropriately prioritized for supplemental screening or preventive interventions. Ultimately, clustering may offer a pathway toward culturally and demographically sensitive breast cancer screening paradigms.

Table 1. Characteristics of the cohort selected from the HIPIMR.

|                   |                     | Cases | Controls |
|-------------------|---------------------|-------|----------|
| Women, N          |                     | 1,307 | 3,779    |
| Age at first exam | 40-49               | 336   | 784      |
|                   | 50-59               | 430   | 1,221    |
|                   | 60-69               | 395   | 1,303    |
|                   | 70-79               | 146   | 471      |
| Race/ethnicity    | NHPI                | 299   | 829      |
|                   | White               | 232   | 592      |
|                   | Chinese             | 98    | 230      |
|                   | Filipino            | 163   | 236      |
|                   | Japanese            | 462   | 815      |
|                   | Other/NOS Asian     | 47    | 1,013    |
| Breast density    | Other               | 6     | 64       |
|                   | Fatty (A)           | 35    | 98       |
|                   | Scattered (B)       | 620   | 1,247    |
|                   | Heterogeneous (C)   | 524   | 1,954    |
|                   | Extremely dense (D) | 128   | 480      |

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## The psychosocial and health service impact of breast density notification — findings from Australia's screening program-embedded randomised controlled trial

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**Introduction:** The ongoing international debate about the benefits and harms of implementing population-based breast density notification lacks robust outcomes data. **Objective:** This trial investigated the effect of notifying women of their dense breasts on their psychosocial outcomes and health service use intention.

**Methods:** Multi-site parallel arm randomised controlled trial conducted within the population-based breast screening program in Queensland, Australia. Women aged  $\geq 40$  years classified as having mammographically-dense breasts (BI-RADS C and D) were randomised equally to standard care (control: no notification of breast density), notification of breast density plus a hard-copy written health literacy-sensitive information (intervention-1), or notification of density plus a link to online written and video-based health literacy-sensitive information (intervention-2). Main outcome measures were psychological (feeling anxious, confused or informed) and health service use intentions (general practitioner (GP) consultation related to breast density, supplemental screening) at 8 weeks post-screening. A sub-set of women in intervention-1 and 2 also completed qualitative semi-structured interviews. **Results:** Between September 2023 and July 2024, 3107 women were randomised, with 2401 women (802 in the control, 776 in intervention-1 and 823 in intervention-2) with a mean age at baseline of 57.4 years (SD 9.9) included in the analysis. Compared to the control, women who were notified of their dense breasts via intervention-1 and -2 reported feeling significantly more anxious (OR=1.20, 95%CI: 1.01-4.43;  $p=.04$ ) and confused (OR=4.04, 95%CI: 2.83-5.76;  $p<.001$ ), and had significantly higher intentions to talk to their GP (RRR=1.89, 95%CI: 1.48-2.42;  $p<.001$ ) and go for supplemental screening (RRR=2.24, 95%CI: 1.50-3.35;  $p<.001$ ). although the majority of women do not intend to undergo supplemental screening (91.3% vs 83.9%). There was no evidence that women who were notified of their dense breast felt more informed (OR=0.91, 95%CI: 0.70-1.18;  $p=.48$ ). **Conclusions:** Women notified of their dense breasts are confused, do not feel more informed to make decisions regarding their breasts, and although significant, may have little consideration for supplemental screening outside of an organised breast screening program and want to be guided by their GPs. **Key finding:** Population-based breast density notification may have adverse outcomes for women and the health service which may warrant further consideration in countries outside of the United States currently contemplating notification. **Impact on screening strategies:** Additional data on beneficial clinical pathways and careful planning of the provision of breast density information in the context of other risk factors for women are needed to ensure that the benefits outweigh any potential harms.

## Clinical guidelines for the management of mammographic density: a systematic review of breast screening guidelines worldwide

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**Introduction:** As countries internationally begin to implement or consider the implementation of breast density notification, there is a need to examine the existing evidence-based guidelines in order to support healthcare professionals to have discussion about supplemental screening with women with dense breasts.

**Objectives:** This systematic review synthesizes the international clinical guidelines, and the evidence base for screening and supplemental screening recommendations in women with dense breasts. **Methods:** A systematic search of CINHAL, Embase, and Medline databases was performed in August 2023 and grey literature searched in January 2024. Two authors independently assessed study eligibility and quality (Appraisal of Guidelines for Research and Evaluation II instrument). **Results:** Of 3809 articles, 23 guidelines published from 2014 to 2024 were included. The content and quality varied between the guidelines; the average AGREE II total score was 58% (range = 23%-87%). Most guidelines recommended annual or biennial screening mammography for women more than 40 years old with dense breasts (n = 16). Other guidelines recommended breast tomosynthesis (DBT, n = 6) or magnetic resonance imaging (MRI, n = 1) as the preferred screening modality. One third of the guidelines (n = 8) did not recommend supplemental screening for women with dense breasts. Of those that recommended supplemental screening (n = 14), ultrasound was the preferred modality (n = 7), with MRI (n = 3), DBT (n = 3), and contrast-enhanced mammography (n = 2) also recommended. Most guidelines described the benefits and harms of supplemental screening; however, none described the environmental impact of imaging. **Conclusion:** Consensus on supplemental screening in women with dense breasts is lacking. The quality of the guidelines is variable, and recommendations are based largely on low-quality evidence. **Key finding:** As evidence of the benefits versus harms of supplemental screening in women with dense breasts is evolving, it is imperative to improve the methodological quality of breast cancer screening and supplemental screening guidelines. **Impact on screening strategies:** This review highlight gaps limiting evidence-based practice and evaluates the implications for breast cancer screening programs worldwide.

## Equity in breast density notification: exploring the impact and needs amongst culturally and linguistically diverse (CALD) women

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**Introduction:** Our previous systematic review suggests a one-size-fits-all approach to breast density notification may disadvantage culturally and linguistically diverse (CALD) women. **Objectives:** This study aimed to qualitatively explore CALD women's understanding and views of breast density, attitudes towards health services access, acceptability of notification and preferences for breast density communication ahead of population-based notification in Australia. **Methods:** Online focus groups were conducted with CALD women of breast screening age (40-74 years) who spoke one of the five languages with the lowest English proficiency in Australia (Korean, Mandarin, Cantonese, Vietnamese and Arabic). Focus group sessions were in-language and incorporated an evidence-based presentation interspersed with group discussions which were audio-recorded, transcribed and analysed thematically. **Results:** Thematic analysis revealed four themes indicating participants had overall strong desires to be informed of breast density, despite some associated worry. CALD women may also face significant barriers to understanding and accessing breast density information and seeking supplemental screening. **Conclusion:** Although CALD women have a strong desire to be notified of their breast density, increased anxiety and confusion may exacerbate health inequalities and barriers women from these communities already face. **Key finding:** Equitable screening pathways for all women related to breast density notification are needed. **Impact on screening strategies:** There is still a need for careful consideration of breast density and supplemental screening communications for CALD women in Australia and other jurisdictions.

## RoBiN: An acceptability and feasibility study of personalised screening

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**Introduction:** Population-based age stratified breast screening and surveillance programs based on risk due to family history of breast cancer are limited. Both approaches fail to consider people unaware of their family history or genetic predisposition and those at risk due to other independent risk factors (*e.g.* breast density) strongly associated with increased risk. Majority of individuals who develop breast cancer do not have a family history<sup>1</sup>, the integration of genomic and traditional epidemiology allows for a holistic approach to understanding breast cancer risk and tailored screening<sup>2</sup>. **Objective:** The study aims to evaluate the acceptability, feasibility and psychological impact of offering risk-based screening recommendations using a risk model which incorporates breast density and a genomic test to women attending routine screening. **Methods:** RoBiN will recruit 150 Australian women aged 40-59 attending BreastScreen Victoria. DNA will be collected with an oral swab to calculate a breast cancer polygenic risk score (PRS). Clinical and genomic risk factors will be combined to calculate 10-year and lifetime risk of breast cancer using the validated BRISK<sup>3</sup> model. The calculated risk will be mapped onto risk categories defined by Cancer Australia and used to tailor supplemental and subsequent breast cancer screening. Participants and a nominated primary care physician will receive a risk report summarising their breast cancer risk, recommendations for any supplemental screening or changes to frequency of subsequent screening. **Conclusion:** Pilot implementation studies can evaluate acceptability and feasibility to address health system readiness for personalised screening<sup>4</sup> in ways yet to be tested in Australia at a population level. Risk models which incorporate clinical and genomic breast cancer risk factors allow for a systematic approach to identify those at increased risk and determine appropriate referral; potentially transforming screening practices. **Key finding:** Australian data indicates that women are ready for a more personalised approach and open to risk-based breast cancer screening<sup>5</sup>. Accurate risk-stratification will allow resources to be reallocated, increasing the efficiency within already struggling healthcare systems<sup>6,7</sup>. **Impact on screening strategies:** The BreastScreen Australia National Policy and Funding Review currently underway, provides a unique opportunity to integrate new evidence into routine practice. Only 50% of the targeted women participate in the Australian national program<sup>1</sup>. Breast cancer risk stratification of women in the general population starting at age 40 would facilitate individualised and informed decision making on screening, lifestyle changes and prevention therapies. Data generated from RoBiN will be used to inform future larger implementation trials, and ultimately inform policy and practice in the Australian screening program.

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## Considerations for simplifying breast density and risk assessment in primary care

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**Introduction:** Breast density reporting is increasing internationally<sup>1,2</sup>. In some jurisdictions, women notified they have dense breasts are directed to see a doctor to discuss their breast health, putting the onus on doctors to determine an appropriate referral pathway. This is despite the lack of clear and consistent information available when consulting women with dense breasts<sup>3,4</sup>. **Objective:** This project aims to co-design a primary care pathway that simplifies supplemental and screening recommendations, and the downstream management of women notified of their breast density. **Methods:** Studies on the diagnostic performance (sensitivity, specificity and positive predictive values)<sup>5-7</sup> of imaging systems for breast density were used to co-develop evidence-based guidance for supplemental imaging pathways based on breast density and categorised by risk due to family history of breast cancer. Referral pathways were co-developed with primary care physicians (PCPs), radiologists, researchers and consumers, including input from breast screening services. **Conclusion:** While more data is needed to evaluate the performance of supplemental screening tests for women with dense breasts, co-developed primary care pathways guided by existing international evidence and local service availability could test imaging modalities (e.g. tomosynthesis, ultrasound, MRI and CEM) across targeted risk groups. Breast density, when considered in the context of the individual's overall risk of breast cancer, will allow for better identification and management of those who would benefit from a comprehensive risk assessment and/or supplemental imaging and informed decision making, to increase cancer prevention and detection. The barriers to the implementation of risk-based screening are well defined within literature, and these challenges can be addressed through the development of accessible consistent guidelines, policies and professional education<sup>8</sup>. **Key finding:** Primary care providers are limited by existing guidelines<sup>9</sup>, creating a fragmented approach to patient management across the wide range of medical, health and diagnostic services. **Impact on screening strategies:** The BreastScreen Australia National Policy and Funding Review, currently underway, provides a unique opportunity to integrate new evidence into routine practice. Pragmatic and clear management pathways, policies and education will allow primary care providers to provide the best evidence-based care for their patients and evaluate risk-based screening to futureproof the Australian national screening program.

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## A physical breast perfusion phantom for validating background parenchymal enhancement quantification in x-ray imaging

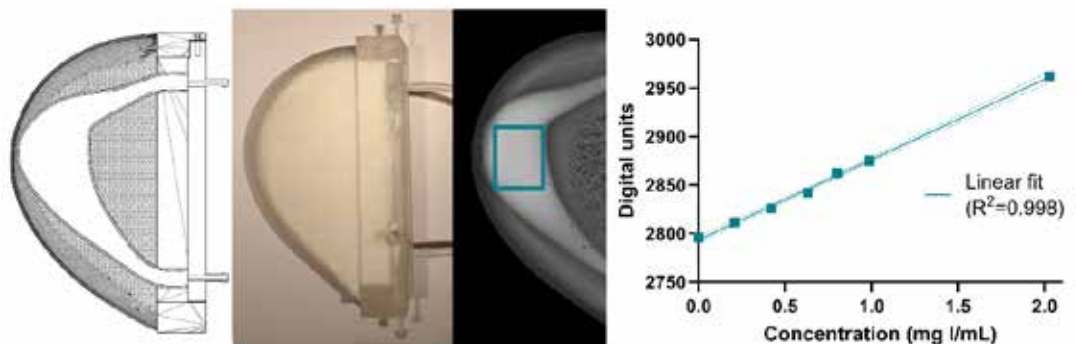
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**Introduction:** Background parenchymal enhancement (BPE) is a known biomarker for cancer development risk and neoadjuvant chemotherapy response. BPE is typically assessed visually in MRI, posing variability in interpretation. Quantitative BPE assessment methods are emerging, including for x-ray imaging modalities, which offer benefits like direct iodine quantification and wider accessibility. **Objectives:** This study aims to develop a physical breast perfusion phantom that includes different known amounts of BPE for contrast-enhanced spectral mammography (CESM) to serve as a test object for optimization and validation of quantitative BPE assessment. **Methods:** The phantom consists of a 3D-printed shell, modelled after the average compressed breast,<sup>1</sup> with a shell thickness of 1.5 mm of clear resin to represent skin, and is filled with coconut oil to simulate fatty tissue. A fillable 3D-printed fibroglandular tissue (FGT) insert, based on a patient model of FGT distribution,<sup>2</sup> is added to the phantom and allows for static and dynamic imaging. For intensity-based assessment, the FGT insert was filled with water with varying iodine concentrations (0, 0.2, 0.4, 0.6, 0.8, 1, and 2 mg I/mL). Volume-based enhancement assessment can be simulated by filling the FGT insert with varying numbers of sodium alginate beads, mimicking non-enhancing FGT, and contrast-containing water. The phantom with the several iodine concentrations was imaged with a clinical CESM system (low energy: 29 kV/90 mAs; high energy: 49 kV/50 mAs), and the recombined (iodine only) images were retrieved. A region of interest was placed at the center of the FGT insert (Fig. 1) to determine the relationship between digital units vs. concentration. **Results:** The FGT insert was properly filled with different iodine concentrations. However, some air was trapped in the coconut oil on the posterior side of the phantom during solidification. A linear BPE intensity gradient across iodine concentration levels was found ( $R^2=0.998$ ) (Fig. 1). **Conclusion:** The phantom allows for known BPE simulation in CESM, providing a potential tool for standardizing BPE assessment in clinical imaging. The next step involves simulating various levels of volume enhancement, which will be completed before the conference. The phantom is also suitable for CE-digital breast tomosynthesis and for dynamic BPE imaging studies, which will be also evaluated in the future. Key finding: The ability to modulate BPE intensity and volume offers a reliable foundation for exploring quantitative BPE markers. Impact on screening strategies: This research supports advancing BPE quantification in x-ray modalities, potentially enhancing breast cancer risk stratification and treatment response assessment.

Figure 1. Design, fabrication & CESM image of the compressed breast phantom with fibroglandular tissue insert (Left). Concentration VS the mean value of the ROI in CESM (Right).



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## High breast density — Why I am a loser in the Australian health care lottery

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### High breast density delayed my breast cancer diagnosis

High breast density has significant implications for breast cancer risk and the inequities within the Australian healthcare system. Despite my long-term commitment to regular screenings through BreastScreen, I was diagnosed with Stage 3 breast cancer due to my high breast density, which masked my cancer during routine mammograms.

BreastScreen, a free Australian government-funded service, is available for women aged 50-74, yet in Victoria, it did not inform clients or their GPs about breast density. If I had lived in South Australia or Western Australia, I would have received critical information about my breast density and its implications for cancer detection. Such knowledge could have prompted my GP to order additional ultrasounds, potentially leading to an earlier diagnosis.

The inequity in access to supplementary screenings like 3D mammograms and ultrasounds exacerbates this issue, as many women cannot afford these extra tests. My personal experience highlights a broader problem in the healthcare system, often referred to as the “**postcode lottery**.” Access to quality health services varies greatly depending on where one lives, impacting equitable care.

Even as a healthcare professional advocating for equitable access, I was surprised to find myself falling through the cracks. The ideal healthcare scenario is to receive the right service at the right time in the right place, but my situation exemplifies how living in the wrong area led to inadequate screening.

### Mending the health care system gaps

Experts agree that merely reporting breast density to patients and GPs is insufficient. The Australian Government is contemplating a risk-based screening model<sup>1</sup>, which could enhance awareness and provide better care. Women should be informed about their breast density, as this is a necessary step toward improving screening processes, although it will require additional funding and resources.

Despite overcoming the challenges, my journey has not ended. After undergoing a mastectomy, chemotherapy, and radiotherapy, I remain hopeful about my future, thanks to the support from a dedicated multidisciplinary healthcare team.

It continues to be crucial for consumers to advocate for improvements in the healthcare system and fill the cracks to ensure all women receive equitable and effective breast cancer care.

(1) ROSA (Roadmap to Optimising Screening in Australia) Breast project

<https://www.cancer.org.au/about-us/policy-and-advocacy/early-detection/breast-cancer/rosa/roadmap>

## Comparison of PAM50 molecular subtype distribution between screen-detected and clinically detected invasive breast cancers in the Malmö Breast ImaginG database

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**Introduction:** Mammography interpretation relies mainly on structural information in images and does not fully address the heterogenous nature of breast cancer and possibilities to provide prognostic and treatment predictive information. Recent technologies made it possible to extract significantly more information from mammography images. To further advance breast cancer imaging research, we compiled the Malmö Breast ImaginG (M-BIG) database, featuring digital mammography and tomosynthesis examinations [1]. **Objectives:** To describe the PAM50 molecular subtypes and the clinicopathological characteristics of cancers included in the M-BIG database. The descriptive information will be further utilized to develop molecular subtype specific risk prediction models. **Material and methods:** The M-BIG database features digital mammography (450,000) and breast tomosynthesis (20,000) examinations performed at the mammography clinic in Malmö between 2004 and 2020. These examinations include screening, diagnostic procedures, preoperative tumor localizations, and specimen examinations. Cancers included in the database were identified through record linkage with regional and national cancer registers, and classified as screening or clinically detected. PAM50 molecular subtype information from RNA sequencing of a subgroup of the invasive cancers was retrieved via the Sweden Cancerome Analysis Network — Breast (SCAN-B) [2]. Clinicopathological and follow-up data, as well as information on adjuvant medical treatment, were obtained from the National Quality Registry for Breast Cancer — Sweden. The current study is approved by the Swedish Ethical Review Authority. **Results:** A total of 4,622 invasive breast cancers were identified between 2010 – 2020, of which 47.5% were screen-detected. The majority of these cancers were ER-positive (84.1%), PR-positive (70%) and HER2-negative (73.9%). Transcriptome data were available for 2,096 tumors, of which 45.6% were screen-detected. The PAM50 molecular subtype distribution was: Luminal A (37.7%), Luminal B (26.0%), HER2-enriched (12.2%), Basal-like (9.5%) and Normal-like (14.4%). In the age groups invited to screening, 40 to 74 years, clinically detected cancers showed a higher proportion of aggressive molecular subtypes, namely Basal-like and HER2-enriched, compared to screen-detected cancers ( $p < 0.001$ ). **Conclusion:** As expected, preliminary investigations in this large cohort revealed a significant difference in the intrinsic molecular subtype distribution between screen-detected and clinically detected cancers. **Key finding:** We have developed a radiography image-based research database enriched with histopathological and transcriptomic data. **Impact on screening strategies:** Well-annotated databases are a key resource for breast cancer research. This project represents an initial step in developing subtype-specific breast cancer risk prediction models to aid in early detection of fast growing, aggressive tumors.

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The Impact of GLP-1 Utilization on Breast Density and Cancer Risk: A Propensity-Matched Retrospective Cohort Study

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**Introduction:** Patients with increased breast density are known to be at increased risk of breast cancer, and their cancers may be more difficult to identify during routine screening mammography. [1,2] GLP-1 agonists can dramatically impact body composition, but studies have not yet proven an impact on breast density or cancer. **Objectives:** The purpose of this study was to use the TriNetX platform to determine if treatment with GLP-1 agonists is associated with a change in breast density and an increased risk of breast cancer. **Methods:** The TriNetX Global Collaborative network was used for this study. Two cohorts of patients were created by utilizing ICD-10 codes and RxNorm medication codes. Both consisted of female patients over age 40 who had a body mass index between 30 and 39, and who did not have a preexisting diagnosis of dense breasts (R92.30). One cohort had been treated with any of the five main GLP-1 agonist medications (semaglutide, tirzepatide, exenatide, liraglutide, or dulaglutide) while the other was prohibited from such treatment. The cohorts were balanced by propensity score matching and the greedy nearest neighbor algorithm for age, race, ethnicity, and existing diagnosis of vitamin D deficiency (E55). This resulted in 219,642 patients in each arm. They were then compared for the outcomes of a future diagnosis of dense breasts and future breast cancer (C50). **Results:** GLP-1 use was associated with a statistically significant increase of both a new diagnosis of dense breasts (1,173 patients versus 0 patients, P value <0.0001) and a small increased risk of breast cancer (3.6% versus 3.4%, risk ratio 1.06, 95% CI (1.03,1.10), P value 0.0001). See Table 1.

| Cohort   | Cohort Size | Dense Breasts | Dense % | Breast Cancers | Breast Cancer % |
|----------|-------------|---------------|---------|----------------|-----------------|
| GLP-1    | 219,642     | 1,173         | 0.53%   | 8,012          | 3.6%            |
| No GLP-1 | 219,642     | 0             | 0%      | 7,544          | 3.4%            |

Table 1. New diagnoses of dense breasts and breast cancers for the two cohorts.

**Conclusion:** Use of GLP-1 agonists is associated with a small but statistically significant increased likelihood of being diagnosed with dense breasts and a 6% increased risk of future breast cancer. **Key Finding:** GLP-1 agonists are effective at altering body composition, including breast tissue density. Because dense breasts were diagnosed in 0.5% of the treated patients and there was a 6% increased risk of breast cancer, the cancer risk may not be directly related to breast density change. **Impact on screening strategies:** This study suggests that patients intending to take GLP-1 agonists may benefit from counseling regarding the above risks, and compliance with annual breast cancer screening for these patients should be emphasized. The use of additional imaging modalities, such as ultrasound or MRI, may be beneficial in some patients.

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## The Potential Relationship Between Breast Density and Vitamin D Deficiency in Premenopausal and Postmenopausal Patients.

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**Introduction:** Multiple studies have attempted to evaluate a potential relationship between breast density and vitamin D levels, but the results have been inconclusive. [1] One study suggests that higher levels of vitamin D intake may be associated with lower breast density. [2] **Objectives:** The purpose of this study is to use the TriNetX platform to investigate the relationship between breast density and vitamin D deficiency status in two different age groups of women who have a similar body mass index. **Methods:** The TriNetX Global Collaborative Network was used for this study. Four cohorts of patients were created using ICD-10 codes, with both consisting of female patients in the BMI range of 25 to 29.9 to reduce weight as a confounding factor. Two cohorts contained women under age 40, one with and one without dense breasts (R92.30), and two over age 60, one with and the other without dense breasts. The cohorts were balanced by propensity score matching and the greedy nearest neighbor algorithm for age, race, and ethnicity, resulting in 578 patients in each younger cohort and 6,532 patients in each older cohort. The cohorts for each age group were compared against each other for the diagnosis of vitamin D deficiency (E55). **Results:** Patients under age 40 with dense breasts were 61% more likely to have vitamin D deficiency than patients without dense breasts (RR 1.61, 95% CI (1.19,2.18), P value 0.008). For patients over age 60, dense breasts were associated with a 46% increased likelihood of having vitamin D deficiency (RR 1.46, 95% CI (1.38,1.55), P value <0.0001). See Table 1.

| Cohort            | Cohort Size | # Vitamin D Deficient | Risk % |
|-------------------|-------------|-----------------------|--------|
| Dense <40 y/o     | 578         | 95                    | 16.4%  |
| Not Dense <40 y/o | 578         | 59                    | 10.2%  |
| Dense 60+         | 6,532       | 2,176                 | 33.3%  |
| Not Dense 60+     | 6,532       | 1,489                 | 22.8%  |

Table 1. Association between breast density status and vitamin D deficiency for the two cohort groups.

**Conclusion:** Increased breast density appears to be associated with the concomitant presence of vitamin D deficiency, regardless of age group. **Key Finding:** This study suggests a potential relationship between the two issues of dense breasts and vitamin D deficiency status. **Impact on Screening Strategies:** In patients who are found to have dense breasts on routine breast imaging, screening for vitamin D deficiency should also be performed because such patients are at increased risk of having it.

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## Longitudinal Changes in Breast Density Among Korean Women Aged 60 and Older Using Group-Based Trajectory Analysis

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**Introduction:** Breast density is an established risk factor for breast cancer and is generally known to decrease with age. Studies have shown that slower rates of density decline or increasing breast density are associated with a higher risk of subsequent breast cancer. However, longitudinal changes in breast density in older women remain understudied. **Objectives:** This study aimed to evaluate longitudinal trajectories of breast density changes in women aged 60 years or older and to identify risk factors associated with these trajectories. **Methods:** We analyzed data from the Korean National Health Insurance Service Database, which includes biennial mammography screenings and breast cancer related risk factors from 2009 to 2020. Breast density was classified using the four-category Breast Imaging Reporting and Data System (BI-RADS). Group-based trajectory modeling was employed to identify patterns of breast density changes across six biennial screening cycles. Women aged 60 years or older who participated in at least four screenings (first in 2009–2010, last in 2019–2020, and at least two intermediate screenings) were included. Missing breast density data were imputed using a multiple imputation method. Logistic regression was used to examine risk factors associated with increasing or decreasing breast density trajectories. **Results:** Among 674,993 women (mean age: 65.0 years; 51% BI-RADS 1 at baseline), five distinct trajectories of breast density changes were identified (Fig. 1). Groups 1 (18.5%), 4 (36.4%), and 5 (15.4%) exhibited stable density levels throughout the study period, while groups 2 (17.47%) showed increasing trend, and group 3 (12.2%) demonstrated a decreasing trend across six screenings. Comparing group 1 to group 2 (increasing density trajectory), women with the following characteristics were more likely to belong to group 2: younger age, family history of breast cancer, history of benign breast disease, history of hysterectomy, older age at menopause, lower baseline BMI, and BMI reduction during the study period. Conversely, ever using oral contraceptives and having more childbirths were negatively associated with the increasing trajectory. **Conclusion:** This study identified five distinct trajectories of breast density changes over a decade in women aged 60 years and older. Premenopausal risk factors, BMI, and BMI changes were significantly associated with long-term changes in breast density. **Key finding:** In women aged  $\geq 60$  years, diverse patterns of breast density changes were observed, including persistent fatty or dense breasts, decreasing density, and even increasing density. **Impact on screening strategies:** Women with risk factors for increasing breast density trajectories may benefit from additional tools to assess breast cancer risk and guide personalized screening strategies.

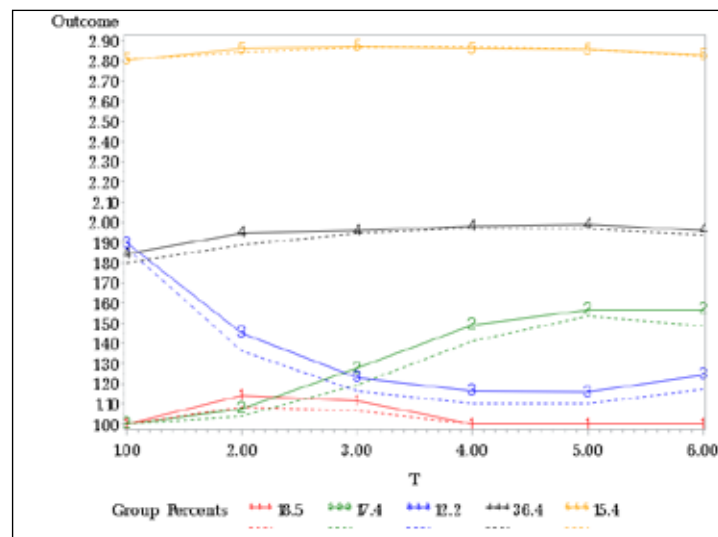


Fig 1. Trajectories of breast density change during six biennial mammography screenings in women aged  $\geq 60$  years

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## Notification of breast density to South Australian women attending breast cancer screening: overcoming misconceptions and addressing psychosocial concerns

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**Introduction:** There is growing awareness of breast density in women attending breast cancer screening, however, the psychological impact of breast density notification is still unclear. **Objectives:** This study aimed to (1) evaluate breast density knowledge of South Australian women, (2) assess the psychological impact of breast density notification, and (3) explore strategies to optimally communicate information to women. **Methods:** This cross-sectional mixed methods study was conducted in women undergoing breast cancer screening at The Queen Elizabeth Hospital Breast/Endocrine outpatient department in South Australia. Participants received a questionnaire adapted from BreastScreen Western Australia's breast density knowledge research (1). Women received a breast density notification letter and 7 days later the State and Trait Anxiety Inventory questionnaire was administered with an additional question asking how participants felt after being notified. A subset of this cohort were invited to a telehealth consultation with a breast surgeon. **Results:** Aim 1: Among 350 participants, 61% were familiar with 'breast density' and 57% had 'some knowledge'. Prior breast density notification (OR = 4.99, 95% CI = 2.76, 9.03; p = 0.004), awareness (OR = 4.05, 95% CI = 2.57, 6.39; p = 0.004), younger age (OR = 0.97, 95% CI = 0.96, 0.99; p = 0.02), and English as a native language (OR = 3.29, 95% CI = 1.23, 8.77; p = 0.02) were independent predictors of 'some knowledge'. A significant proportion of participants (82%) expressed desire to ascertain their individual breast density. Aim 2: There were no significant differences in State anxiety scores between women with dense breasts (n=34, 36.65±13.03) and non-dense breasts (n=66, 35.17±13.60, p=0.51). The majority of women reacted positively towards density notification. Aim 3: Thematic analysis of 12 telehealth consultations revealed patients had concerns about breast density-related risks, barriers to screening, risks to family members and previous screening experiences, which at times were compounded by misunderstandings. Surgeons addressed these concerns through providing further information and reassurance.

**Conclusions:** When notifying women of their breast density, the information should be provided in a manner considerate of their knowledge, range of experiences and circumstances. **Key findings:** Breast density knowledge of this cohort was generally quite low and common misconceptions still exist. Breast density notification was not associated with elevated State anxiety; however, many women had underlying severe Trait anxiety. **Impact on screening strategies:** Co-design of communication strategies with consumers and clinicians may help mitigate any misconceptions or negative reactions to breast density notification.

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## Distribution of invasive and advanced breast cancer risk by breast density

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**Introduction:** Established models predicting short-term risk of invasive and advanced breast cancer may help direct supplemental breast cancer screening to women who are most likely to benefit, including women with dense breasts. The distributions of invasive and advanced cancer risk across breast density categories have not been previously compared. **Objectives:** We sought to characterize the distribution of invasive and advanced breast cancer risk among women undergoing mammography screening according to breast density. **Methods:** We used observational data from 756,971 women aged 40-74 years undergoing mammography screening at facilities within the Breast Cancer Surveillance Consortium in the United States. We calculated 5-year risk of invasive breast cancer and 6-year cumulative risk of advanced cancer using established BCSC risk prediction models (<https://www.bsc-research.org/index.php/tools>) and applied previously established risk thresholds to classify women as low/average vs. intermediate/high risk. **Results:** Among all women, the Spearman correlation coefficient between the two risk models was 0.75. 32.4% of women were identified as having intermediate/high ( $\geq 1.67\%$ ) 5-year invasive cancer risk and 31.8% had intermediate/high ( $\geq 0.38\%$ ) advanced cancer risk. 21.1% of women had intermediate/high risk on both models, whereas 22.0% had intermediate/high risk on one model but not the other, and 56.8% had low/average risk on both models. The prevalence of intermediate/high invasive breast cancer risk increased across breast density categories, ranging from 9.1% among women with almost entirely fatty breasts to 38.0% among women with extremely dense breasts. The prevalence of intermediate/high advanced cancer risk increased to a greater extent across breast density categories, ranging from 0.2% among women with almost entirely fatty breasts to 49.5% among women with extremely dense breasts. Within the full study population, 57.6% of women with intermediate/high 5-year invasive breast cancer risk had dense breasts, compared with 70.1% of women with intermediate/high 6-year advanced cancer risk. **Conclusion:** Invasive and advanced cancer risk increase with increasing breast density category with a larger fraction of women with intermediate/high advanced cancer risk than intermediate/high invasive cancer risk having dense breasts. **Key finding:** There is a strong correlation between risk of invasive and advanced breast cancer with established BCSC risk models, yet cross-classification analyses reveal substantial differences in intermediate/high risk classification overall and according to breast density. **Impact on screening strategies:** Supplemental screening strategies that target interventions based on 6-year advanced cancer risk is more likely to identify women at intermediate/high risk with dense breasts compared to strategies based on 5-year invasive breast cancer risk.

## Regional Disparities in Advanced-Stage Breast Cancer Across the Hawaiian Islands: Insights from the Hawaii and Pacific Islands Mammography Registry

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**Introduction:** Despite recent advances in early detection and treatment, breast cancer remains a major cause of morbidity and mortality in the U.S. Notable racial/ethnic differences in incidence and survival have been described<sup>1</sup>. Further, the percentage of advanced stage breast cancers are considerably higher in U.S. Associated Pacific Islands compared to the U.S. mainland at 49% and 34%, respectively<sup>2</sup>. We present the Hawaii and Pacific Islands Mammography Registry (HIPIMR), which contains data from over 124,475 women undergoing breast imaging in the state of Hawaii. Included are demographic, residential, clinical, and pathologic characteristics, and cancer outcomes obtained through HIPIMR data as well as linkage with the Hawaii Tumor Registry.

**Objectives:** In this study we asked if advanced-stage breast cancer rates differed by region within each island.

**Methods:** Women who participated in mammographic screening in the HIPIMR between 2009-2019 were grouped by their residential address into the following regions: Big Island, Maui, Kauai Region (including Molokai and Lanai), 4 divisions of Oahu using zip code groupings (central, Honolulu, leeward, windward) and unknown region. Advanced-stage rates between subgroups of interest were compared with chi-square tests of independence ().

**Results:** Currently the HIPIMR contains 124,475 unique women with visits from 2009 to 2024, and of those a total of 5,511 women had invasive cancer during this period. Advanced-stage rates were as follows: Big Island 36%, Maui 21%, Kauai Region 39%, Central Oahu 32%, Honolulu 35%, Leeward Oahu 38%, Windward Oahu 32% and Unknown 40%. The pairwise comparisons showed a significant difference ( $p < 0.001$ ) (between Honolulu and Big Island, Kauai, Windward). No significant differences were found between the other regions.

**Conclusion:** Within the HIPIMR, the advanced-stage breast cancer rate is not uniform across Hawaii, with Kauai Region experiencing the highest proportion of advanced cancers 44% while the lowest proportion was observed for Maui at 22%. The advanced-stage cancer rate in Honolulu significantly differed from many of the more rural islands such as Big Island, and Kauai Region.

**Key findings:** Advanced-stage breast cancer rates vary significantly across Hawaii, with some rural regions such as Kauai Region and the Big Island showing higher rates compared to urban Honolulu, highlighting potential disparities in breast health screening services.

**Impact on screening strategies:** The regional disparities across the different islands highlight the need to focus screening efforts on areas with high advanced-stage breast cancer.

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# The Gut Microbiome and Breast Mammographic Density in the Multiethnic Cohort Study

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**Introduction:** The gut microbiota may influence breast cancer risk through the modulation of immune system activity, the alteration of estrogen levels, and the production of bacterial metabolites. **Objectives:** Whether gut microbial characteristics are associated with percent mammographic density (PMD), a strong predictor of breast cancer risk, is the subject of this analysis. **Methods:** The study population consisted of female participants in the Adiposity Phenotype Study, a subset of the Multiethnic Cohort. Postmenopausal women from five ethnic groups provided a stool sample, from which DNA was extracted and the V1-V3 region of the 16S rRNA gene was amplified and sequenced (MiSeq). As exposure, 152 genera, 10 phyla, and three alpha diversity measures (Shannon, PD Whole Tree, Chao1) were computed. ComBat-adjustment to correct values across laboratory batches and centered log-ratio transformation to account for their compositional nature was applied to all phylum and genus variables. PMD was assessed in routine mammograms taken before stool collection using a quantitative computer-assisted method. General linear models regressed square root-transformed PMD on diversity, phyla, and genera while adjusting for known confounders. To address multiple comparisons, Bonferroni correction was applied. **Results:** Of the 649 women with a mean age of 69.1±2.7 (range: 59.9-77.0) years, 311 had high (≥15%) and 338 had low (<15%) PMD. Participants with high PMD had significantly lower BMI and were more likely to be of Native Hawaiian or Japanese American ancestry than women with low PMD. Measures of alpha diversity and abundance of 10 phyla were not associated with PMD, but 14 genera were significantly related to PMD: 9 positively (*Bacteroides\_Pectinophilus\_group*, *Bifidobacterium*, *Blautia*, *Dialister*, *Eubacterium\_fissicatena\_group*, *Eubacterium\_ruminantium\_group*, *Lachnospiraceae\_Lachnospira*, *Lachnospiraceae\_UCG-008*, *Lachnospiraceae\_uncultured*) and 5 inversely (*Acidaminococcus*, *Ruminococcaceae\_DTU089*, *Alistipes*, *Eubacterium\_oxidoreducens\_group*, *Senegalimassilia*). However, after Bonferroni correction no associations reached statistical significance. **Conclusion:** Despite the small study population and the cross-sectional design, the results suggest that certain gut microbiota may affect PMD through one of several hypothesized biologic mechanisms. For example, bacteria involved in short-chain fatty acid production (*Alistipes*, *Ruminococcaceae*) may lower inflammatory processes and contribute to immunoregulation. As *Senegalimassilia* degrades estrogen-like compounds, it may alter host exposure to hormones. To elucidate possible pathways, future prospective investigations need to include large populations across the lifespan. **Key finding:** It is possible that the gut microbiome composition affects PMD and breast cancer risk. **Impact on screening strategies:** In the distant future, knowledge about the gut microbiome may become a viable option to alter the exposure to steroid hormones associated with PMD.

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**Table. Gut Microbiome Characteristics of APS Participants by Percent Mammographic Density<sup>1</sup>**

| Variable    | Category                        | Low density | High density | β (p-value) <sup>2</sup> |
|-------------|---------------------------------|-------------|--------------|--------------------------|
| Number      |                                 | 311         | 338          |                          |
| a diversity | Shannon                         | 6.5±0.7     | 6.4±0.8      | -0.08 (0.18)             |
|             | PD Whole Tree                   | 23±3.7      | 23±4.1       | -0.001 (0.92)            |
|             | Chao1                           | 1035±143    | 1048±163     | 0.0004 (0.14)            |
|             |                                 |             |              |                          |
| Phyla       | Actinobacteria                  | -0.3±1.3    | -0.3±1.4     | 0.02 (0.55)              |
|             | Bacteroidetes                   | 4.0±0.9     | 4.0±1.0      | -0.02 (0.64)             |
|             | Cyanobacteria                   | -0.7±1.6    | -0.7±1.7     | -0.008 (0.77)            |
|             | Firmicutes                      | 4.3±0.9     | 4.3±1.0      | -0.03 (0.53)             |
|             | Fusobacteria                    | -1.9±2.2    | -1.9±2.2     | 0.01 (0.47)              |
|             | Lentisphaerae                   | -1.2±1.8    | -1.1±1.8     | 0.02 (0.37)              |
|             | Proteobacteria                  | 0.5±1.7     | 0.3±1.6      | 0.02 (0.50)              |
|             | Synergistetes                   | -1.1±1.8    | -1.2±2.0     | -0.01 (0.61)             |
|             | Tenericutes                     | -1.9±2.3    | -2.0±2.2     | 0.002 (0.90)             |
|             | Verrucomicrobia                 | -1.5±2.1    | -1.5±2.1     | -0.03 (0.12)             |
|             |                                 |             |              |                          |
| Genera      | Acidaminococcus                 | -0.1±0.7    | -0.3±0.9     | -0.11 (0.04)             |
|             | Alistipes                       | 3.1±1.4     | 2.8±1.5      | -0.08 (0.01)             |
|             | Bacteroides_Pectinophilus_group | -0.9±1.4    | -0.7±1.3     | 0.07 (0.04)              |
|             | Bifidobacterium                 | -0.5±1.5    | -0.3±1.6     | 0.06 (0.03)              |
|             | Blautia                         | 3.8±0.7     | 4.0±0.8      | 0.12 (0.04)              |
|             | Dialister                       | -0.7±1.9    | -0.5±2.0     | 0.05 (0.03)              |
|             | Ruminococcaceae_DTU089          | -1.2±1.2    | -1.2±1.3     | -0.07 (0.05)             |
|             | Eubacterium_fissicatena_group   | -1.5±1.3    | -1.3±1.3     | 0.07 (0.04)              |
|             | Eubacterium_oxidoreducens_group | -0.4±1.5    | -0.7±1.6     | -0.06 (0.04)             |
|             | Eubacterium_ruminantium_group   | -1.0±1.5    | -0.9±1.6     | 0.06 (0.04)              |
|             | Lachnospiraceae_Lachnospira     | 0.0±1.6     | 0.3±1.7      | 0.07 (0.01)              |
|             | Lachnospiraceae_UCG-008         | 3.5±0.6     | 3.5±0.6      | 0.16 (0.02)              |
|             | Lachnospiraceae_uncultured      | 1.8±1.0     | 1.9±1.0      | 0.10 (0.02)              |
|             | Senegalimassilia                | -0.4±1.1    | -0.6±1.3     | -0.11 (0.002)            |

<sup>1</sup>Values represent mean±SD  
<sup>2</sup>Regression coefficients (β) and p-value obtained from general linear models with percent mammographic density as dependent variable and adjusted for age at clinic visit and ethnic group, BMI, physical activity, antibiotic treatment, alcohol intake, smoking status, number of children, and family history of breast cancer

## Cell-type aware transcriptome-wide association study of mammographic density phenotypes

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**Introduction:** Mammographic density (MD) phenotypes are highly heritable and strongly associated with breast cancer risk. Genetic variants identified by genome-wide association studies (GWAS) explain only a small fraction of the heritability, and the responsible genes remain largely unknown. Transcriptome-wide association studies (TWAS) can improve the power of GWAS and identify genes associated with MD through their genetically regulated gene expression levels. However, cell-type heterogeneity in bulk tissue samples can obscure disease associations. **Objectives:** This study aims to conduct TWAS of MD phenotypes using standard approaches and a novel cell-type-aware framework. **Methods:** The study population included 24,158 women of European ancestry who underwent screening with Hologic (n=20,282) or GE (n=3,876) digital mammography and participated in the Research Program on Genes Environment and Health (RPGEH) at Kaiser Permanente Northern California. Dense area (DA), nondense area (NDA), and percent density (PD) were measured centrally using Cumulus6. Gene expression was estimated using a PrediXcan model for bulk mammary tissue, and a novel method (MiXcan) that estimates cell-type-specific expression for mammary epithelial vs. non-epithelial (stromal) cells. The genetically predicted gene expression levels were then assessed for their associations with MD phenotypes in linear regression models adjusted for age, BMI, and other covariates. Significance was determined by controlling the false-discovery rate at 0.05. **Results:** Standard TWAS methods generally had higher power than the more complex cell-type-aware models when there was little evidence of cell-type heterogeneity, identifying a total of 30 vs. 9 significant genes. However, MiXcan uniquely identified one cell-type-specific gene, ZNF703, whose expression levels in stromal vs. epithelial cells were more strongly associated with NDA and PD. Adipocytes are the predominant stromal cell type in the breast, and ongoing work to be presented at the meeting will develop mammary adipocyte cell-type-specific models and compare the results with mammary and adipose bulk-tissue models. **Conclusion:** This TWAS identified novel genes for MD phenotypes, and prioritized genes at known GWAS loci that are likely to be causally associated with MD phenotypes through their genetically regulated gene expression levels in mammary epithelial and stromal cells. **Key finding:** Disentangling the distinct effects of gene expression in mammary epithelial and adipocyte cells from other cell types through cell-type-aware analysis can yield new gene discoveries and insights into the biological basis of dense vs. nondense breast tissue. **Impact on screening strategies:** Genetic predictors of MD phenotypes can be incorporated into breast cancer risk models to improve personalized risk assessment and screening.

## Asymmetry in breast density and risk of breast cancer among Black American women

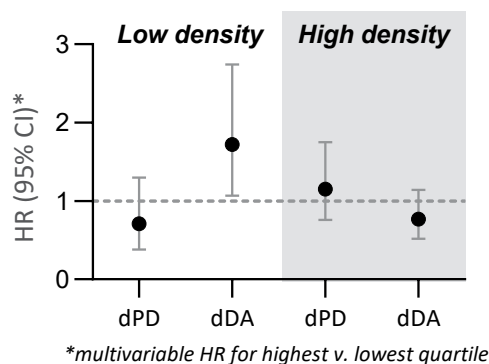
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**Introduction:** High breast density is a strong risk factor for breast cancer; however, density asymmetry – the difference in density measures between the right and left breast – is understudied (1). While mammographic density asymmetry may reflect image artifact, it could also arise as a consequence of exposure to endogenous or exogenous hormones or may be indicative of a developing mass requiring intervention. **Objectives:** We examined breast density asymmetry and breast cancer risk among Black women living in the United States.

**Methods:** Participants were 5,904 women enrolled in the Black Women's Health Study with digital screening (i.e., pre-diagnostic) mammograms among whom 363 developed breast cancer (cases). We calculated the absolute value of the difference in percent density (dPD) and the difference in absolute dense area (dDA) between the two breasts. We fit Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and body mass index (BMI) at mammography, for the association of dPD and dDA with breast cancer risk. Fully adjusted models additionally included average percent density or average dense area. **Results:** Participants were 56 years of age on average and 71% were postmenopausal at the time of mammography. The median time between mammography and breast cancer diagnosis was 3.2 years (IQR: 1.1-5.7 years). In age- and BMI-adjusted models, women in the highest quartile of dPD had a 23% increased risk of breast cancer compared to those in the lowest quartile (HR 1.23, 95% CI 0.90, 1.67). Further adjustment for average percent density attenuated this association (HR 1.10, 95% CI 0.80, 1.52). For dDA, the corresponding HRs were 1.18 (95% CI 0.88, 1.58) and 1.18 (95% CI 0.87, 1.58). However, in the subgroup of women with low average percent density (dichotomized at the median), greater dDA was associated with increased breast cancer risk (HR 1.72, 95% CI 1.07, 2.74) (Figure 1). **Conclusion:** Density difference measures were not associated with breast cancer risk overall; however, an increased risk was observed for dDA among women with low average percent density. **Key finding:** Asymmetry in breast density does not appear to increase risk beyond average density alone, except possibly among women with relatively low percent density. **Impact on screening strategies:** Average percent breast density is likely a sufficient marker for increased breast cancer risk among Black women.

Figure 1. Association of dPD and dDA with breast cancer risk, by strata of percent density.



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## Body Fat, inflammation, and physical activity: insights into breast tissue composition in adolescent girls

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**Introduction:** Higher adiposity is associated with lower mammographic breast density in adult women,<sup>1,2</sup> but the relationship between body fat and breast tissue composition (BTC) in adolescents is less understood. It is also unclear whether chronic inflammation and oxidative stress, consequences of higher body fat,<sup>3,4</sup> or physical activity, a modifiable factor that can reduce body fat, influence BTC during this developmental period.

**Objectives:** To investigate the associations of body fat, inflammation, oxidative stress, and physical activity with BTC in adolescent girls.

**Methods:** We analyzed cross-sectional data from 216 Black and Hispanic girls, aged 11–20, in New York City. BTC was measured using optical spectroscopy, which assesses chromophores associated with breast density (water and collagen positively, lipid negatively). Percent body fat was measured using bioelectrical impedance (Omron HBF-360C). Using biospecimens collected at the time of BTC, we measured blood levels of inflammation (TNF- $\alpha$ , IL-6, and hsCRP) and urinary 15-isoprostane F<sub>2t</sub>, a marker of oxidative stress. Girls self-reported participation in organized (e.g., sports) physical activities during the week prior to BTC measurement. Linear regression models, adjusted for age and race/ethnicity, were used to examine associations. All continuous variables were log-transformed and standardized.

**Results:** When examining adolescent BTC (Table 1), higher body fat was associated with lower water content ( $\beta$ : -0.18, 95% CI: -0.30, -0.06), lower collagen content ( $\beta$ : -0.12, 95% CI: -0.25, 0.02), and higher lipid content ( $\beta$ : 0.25, 95% CI: 0.14, 0.36). Higher hsCRP, which was positively associated with body fat ( $\beta$ : 0.55, 95% CI: 0.44, 0.66), was also associated with lower collagen content ( $\beta$ : -0.22, 95% CI: -0.43, -0.01) and higher lipid content ( $\beta$ : 0.18, 95% CI: 0.02, 0.34). Girls who participated in  $\geq 2$  hours/week of organized physical activity had lower body fat ( $\beta$ : -0.44, 95% CI: -0.86, -0.01) and lower water content ( $\beta$ : -0.41, 95% CI: -0.77, -0.05) compared to inactive girls.

**Key Finding:** Consistent with findings in adult women,<sup>1,2</sup> higher body fat in adolescent girls was associated with lower breast density, reflected by lower water and collagen content and higher lipid content. Elevated CRP levels may partially mediate this relationship, suggesting a potential role of inflammation in BTC. Additionally, while body fat was inversely associated with both water content and physical activity, higher physical activity was independently associated with lower water content. This suggests that physical activity may influence BTC through mechanisms unrelated to body fat.

**Conclusion:** BTC during adolescence may be influenced by adiposity and energy balance.

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Table 1. Associations of percent body fat, chronic inflammation, oxidative stress, and organized physical activity with breast tissue composition in adolescent girls

| Predictor                                   | Water Content, %<br>$\beta$ (95% CI) | Collagen Content, %<br>$\beta$ (95% CI) | Lipid Content, %<br>$\beta$ (95% CI) |
|---------------------------------------------|--------------------------------------|-----------------------------------------|--------------------------------------|
| Percent body fat <sup>a</sup>               | -0.18 (-0.30, -0.06)                 | -0.12 (-0.25, 0.02)                     | 0.25 (0.14, 0.36)                    |
| hsCRP <sup>b</sup>                          | 0.06 (-0.13, 0.24)                   | -0.22 (-0.43, -0.01)                    | 0.18 (0.02, 0.34)                    |
| IL-6 <sup>b</sup>                           | -0.01 (-0.16, 0.13)                  | -0.07 (-0.24, 0.09)                     | -0.04 (-0.17, 0.09)                  |
| TNF- $\alpha$ <sup>b</sup>                  | 0.07 (-0.06, 0.19)                   | -0.05 (-0.19, 0.09)                     | 0.03 (-0.09, 0.14)                   |
| 15-isoprostane F <sub>2t</sub> <sup>b</sup> | -0.07 (-0.20, 0.05)                  | 0.15 (0.00, 0.31)                       | 0.01 (-0.11, 0.14)                   |
| Organized physical activity <sup>b</sup>    |                                      |                                         |                                      |
| None                                        | reference                            | reference                               | reference                            |
| < 2 hours/week                              | -0.22 (-0.61, 0.16)                  | -0.14 (-0.58, 0.30)                     | 0.29 (-0.06, 0.64)                   |
| $\geq 2$ hours/week                         | -0.41 (-0.77, -0.05)                 | 0.05 (-0.36, 0.46)                      | 0.12 (-0.21, 0.44)                   |

Abbreviations: hsCRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6, TNF- $\alpha$  = tumor necrosis factor- $\alpha$

<sup>a</sup>Estimates are adjusted for age, ethnicity, and optical spectroscopy device type.

<sup>b</sup>Estimates are adjusted for age, ethnicity, optical spectroscopy device type, and percent body fat.

## Improving Screening Performance by Ordering Mammogram Interpretation Batches Based on Breast Density

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**Introduction:** Interpreting mammograms with complex backgrounds can be challenging, leading to missed cancers or false positives. Ordering mammograms based on image characteristics such as density may enhance radiologists' perception and performance by leveraging visual adaptation, a sensory process that reduces sensitivity to the current visual stimulus (e.g., the image background) and increases the salience of novel stimuli (e.g., a potential lesion). **Objectives:** This study investigates whether ordering screening mammograms by a similarity metric when batch reading can optimize visual adaptation and therefore improve screening performance and/or efficiency. For this, we tested how ordering mammograms by volumetric breast density or using a self-supervised learning (SSL)-based similarity algorithm impacts reader performance. **Methods:** A multi-reader multi-case observer study was conducted, involving 13 breast screening radiologists who interpreted 150 screening digital mammography examinations (1:1 ratio of malignant to normal/benign) in three different orders: (i) random order, (ii) increasing volumetric breast density measured by Volpara® Density™, and (iii) the SSL-based similarity order. Performance metrics, including the area under the receiver operating characteristic curve (AUC), sensitivity, and specificity, were compared between random-ordered readings and those ordered by density or the SSL algorithm using mixed-model analysis of variance. Additionally, reading time and perceived density were compared using Wilcoxon signed-rank tests. **Results:** Radiologists performed better (AUC: 0.934 vs 0.921;  $P=0.009$ ) and read faster (24.3 seconds vs 27.9 seconds;  $P<0.001$ ) when mammograms were ordered by increasing density compared to when ordered randomly (Figure 1). No improvement was found for the SSL-ordered readings (AUC: 0.917 vs 0.921;  $P=0.70$ , reading time: 28.4 seconds vs 27.9 seconds;  $P=0.02$ ). Reading order influenced radiologists' perceived density ( $P<0.001$ ), with images appearing denser when interpreted in order of increasing density, consistent with adaptation to the preceding, less-dense images. **Conclusion:** Organizing batch reading of screening mammograms from low to high breast density shows promise for improving radiologist reader performance and efficiency. **Key finding:** Reading screening mammography examinations ordered from low to high breast density improves screening outcomes, potentially by optimizing the state of the reader's visual adaptation, and appears to improve screening performance and efficiency.

**Impact on screening strategies:** Ordering screening mammograms by increasing breast density could be easily implemented in protocols for batch reading and could lead to earlier diagnosis and improved patient outcomes. Additional features of visual adaptation are continued to be investigated to determine if this sensory process can be leveraged further for further improvements in batch screening image interpretation.

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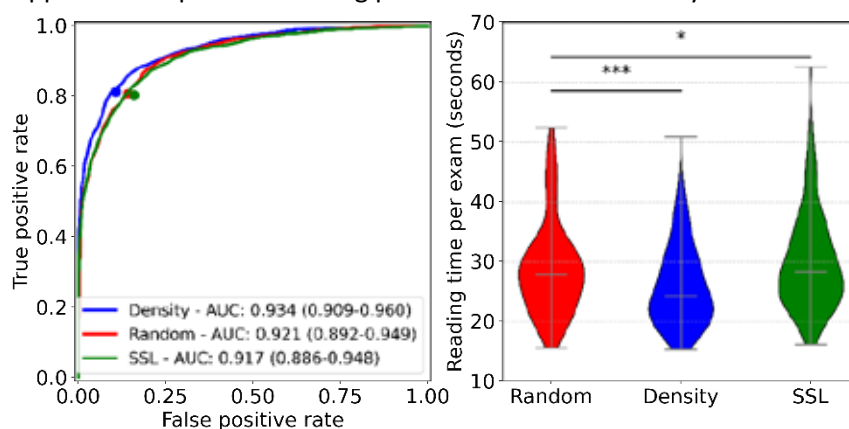


Figure 1. (left) Reader-averaged receiver operating characteristic (ROC) curves and (right) median reading times of the radiologists reading screening mammograms ordered by increasing breast density (blue), randomly (red), and ordered by the self-supervised learning (SSL) algorithm (green). The dots indicate radiologists' operating points based on their recall decisions. \*\*\*  $P<0.0005$ , \*\*  $P<0.005$ , \*  $P<0.025$ .

## Diagnostic accuracy of abbreviated magnetic resonance imaging for breast cancer screening among women with extremely dense breasts: a multi-reader study

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**Background:** Despite proven cost-effectiveness, implementation of MRI in breast cancer screening programs is slowed down by debates about costs and capacity. Costs and time may be reduced by using an abbreviated MRI (AB-MRI) protocol. **Objectives:** The DENSE trial's multiparametric protocol provided the unique opportunity to compare the accuracy of various abbreviated MRI protocols to the full multiparametric MRI protocol, focusing on identifying the minimal protocol necessary to maintain high diagnostic accuracy. **Methods:** Seven radiologists performed incremental reads of a subset of 518 MRI examinations from the DENSE trial (women with extremely dense breasts and negative mammography). Different sequences were added in four incremental steps, starting with: 1) both high resolution (hi-res) and ultra-fast T1-weighted images (T1WI), up to 120 seconds after contrast-injection only, 2) complemented by diffusion-weighted images (DWI), 3) T2-weighted images (T2WI), and 4) finally adding all remaining full protocol sequences: non-fatsat-T1-weighted pre-contrast images, all remaining dynamic phases, and curve-kinetics. Each radiologist assessed the same 518 MRI examinations and provided BI-RADS scores for all four incremental steps. We calculated the pooled sensitivity and specificity across all readers per incremental step by using a generalized estimating equation model, and the pooled reading time per incremental step by using a linear mixed model. **Results:** The sensitivity of the most abbreviated MRI protocol (step 1) was not significantly different from that of the full multiparametric MRI protocol (step 4) ( $p=0.68$ ). Similarly, specificity was not significantly different ( $p=0.39$ ). The pooled reading time of step 1 was almost 50% shorter than that of the full multiparametric MRI protocol ( $p<0.01$ ), the MR acquisition time was 70-80% shorter, depending on hospital and scanner vendor. **Conclusion:** In a screening setting, the sensitivity and specificity of an ultrafast bi-dynamic T1WI-only protocol were not statistically significantly different from those of a full multiparametric MRI protocol, including pre-contrast DWI and T2WI, and delayed post-contrast T1WI. **Key finding:** In a screening setting, the incremental parts of a full multiparametric MRI protocol do not provide significant additional diagnostic information for making a recall/no-recall decision. The reading time and acquisition time of a very short AB-MRI protocol were almost 50% and 70-80%, respectively, shorter than that of the full multiparametric MRI protocol. **Impact on screening strategies:** Short reading- and scan-times and high diagnostic accuracy facilitate implementing AB-MRI as a more sensitive, supplemental screening technique in (national) breast cancer screening programs for women with extremely dense breasts and a negative screening mammogram.

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## Hormonal contraceptive use around menopause and its effect on breast density

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**Introduction:** The use of hormone replacement therapy (HRT) has been associated with increased breast density and breast cancer risk. However, the prevalence of hormonal contraceptive (HC) use around menopause and its effect on breast density and breast cancer risk is unclear. **Objectives:** We aimed to study the prevalence of HC and HRT use around menopause and the association with breast density. **Methods:** In total, 4783 women (49-75 years) with extremely dense breasts and 1206 women (49-60 years) with entirely fatty breasts were recruited from the Dutch mammography screening program. Data on HC use, HRT use, and confounders were collected by self-report questionnaires. Multivariable logistic regression models were used to examine the association of HC use and HRT around menopause with breast density. **Results:** In this Dutch group of women aged 49 and over, a total of 562 (10%) women were current users of HC's, while only 144 women (2%) were current users of HRT. Women who currently used HC were more likely to have extremely dense breasts than women who had never used them; this association was borderline statistically significant (adjusted odds ratio (adjOR), 1.62; 95% confidence interval (CI), 0.99, 2.67). Women who stopped HC's for >2 years were less likely to have extremely dense breasts than current users (adjOR, 0.38; 95% CI, 0.20-0.70). A similar association, although nonsignificant, was observed for current HRT use compared to never use (adjOR, 1.23; 95% CI, 0.58-2.59), but the numbers of current HRT users were very low. **Conclusion:** This study showed that in this Dutch population of women aged 49-75 years, the use of HC's around menopause was much higher than the use of HRT. Additionally, the findings suggest an effect of HC's on breast density of a magnitude comparable to what has been described in the literature for HRT. These findings should be confirmed to guide potential future decisions regarding the use of HC's around menopause. **Key finding:** In this Dutch population of women aged 49-75 years, the use of hormonal contraceptives around menopause was much higher than the use of hormone replacement therapy. **Impact on screening strategies:** Given the comparable effect of hormonal contraceptives on breast density, it may be worth considering discontinuing the use during menopause and discussing alternative options for managing menopausal symptoms.

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## Association between Ultra-processed foods consumption during pregnancy and breast density post-partum: the Chilean Maternal and Infant Nutrition Cohort Study II (CHiMICs-II)

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**Introduction:** The consumption of ultra-processed foods (UPF) has been linked to a higher risk of breast cancer (BC). Breast density (BD) is a well-established modifiable risk factor for BC, with pregnancy itself associated with an estimated 12% reduction in BD per birth. However, it is unclear whether UPF consumption during pregnancy could influence reductions in BD, potentially affecting BC risk.

**Objectives:** This study aims to assess whether UPF consumption during pregnancy is associated with breast composition measures, specifically percent fibroglandular volume (%FGV) and absolute fibroglandular volume (AFGV) after finishing breastfeeding.

**Methods:** The *Chilean Maternal and Infant Nutrition Cohort Study II* (CHiMICs-II) is a longitudinal study of pregnant women (n = 1954) recruited from public healthcare centers in Chile. Participants were followed from their first prenatal visit to three months post-lactation. Dietary intake during pregnancy was assessed via two 24-hour dietary recalls, with UPF categorized using the NOVA classification. Among 344 participants, %FGV and AFGV were measured using dual-energy X-ray absorptiometry (DXA) at least three months post-lactation. Associations between UPF consumption (as % of total kcal and grams in quartiles) and BD measures were analyzed using linear regression models adjusted for age, pregestational BMI, breastfeeding duration, parity, smoking, alcohol intake, education, and total energy intake.

**Results:** The mean age of participants was 29.9 years (SD = 6.0), with 37% having pregestational obesity. Average energy intake was 1,606 kcal/day (SD = 479.1), with 35% of calories and 22.4% of grams from UPF. DXA measurements were performed an average of 204 days post-lactation (SD = 137). By UPF quartiles, mean %FGV and AFGV were 36.0% (SD = 11.1) and 217 cm<sup>3</sup> (SD = 107) in Q1 versus 36.0% (SD = 10.4) and 206 cm<sup>3</sup> (SD = 116) in Q4. No significant associations were observed between UPF quartiles and %FGV or AFGV (e.g., UPF kcal Q4 vs. Q1, adjusted  $\beta$  for %FGV: -2.1, 95% CI -5.0; 0.8).

**Conclusion:** Our findings indicate that UPF consumption during pregnancy was not associated with breast density measures (%FGV or AFGV) in Chilean mothers. Further studies are needed to evaluate the long-term implications of UPF intake during pregnancy on BC risk and other health outcomes. **Key finding:** We did not observe an association between UPF consumption during pregnancy and breast density measures after finishing lactation. **Impact on screening strategies:** Understanding environmental factors, such as diet, as predictors of breast density and BC risk could add information to screening models.

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## Association between Sex Hormones and Breast Composition during and after Puberty.

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**Introduction:** The association between sex hormones and breast density remains unclear, particularly during adolescence when hormonal fluctuations are pronounced. Previous research in young women has linked premenarcheal sex hormone-binding globulin (SHBG) and progesterone to higher percent fibroglandular volume (%FGV), though data on absolute fibroglandular volume (AFGV) is scarce. **Objective:** To evaluate the relationship between endogenous sex hormones during and after puberty and breast composition (%FGV and AFGV) prior to the first full-term pregnancy. **Methods:** This study included 490 participants from a longitudinal cohort of 602 low-income Chilean girls born in 2002-2003. Anthropometric data, breast composition via dual-energy X-ray absorptiometry (DXA), and fasting blood samples for sex hormones (estradiol, testosterone, androstenedione, progesterone, dehydroepiandrosterone sulfate [DHEAS]) were collected at Tanner stage 4, 2 years post-menarche, and 4 years post-menarche. Breast composition measures (%FGV and AFGV) were calculated using a two-compartment model of adipose and fibroglandular tissue (UCSF-developed software). Associations between hormones and breast composition were assessed using linear and mixed-effects regression models, adjusted for birth weight, maternal education, BMI z-score, and age at menarche. **Results:** At Tanner stage 4 (mean age 11.3 years), 53.3% of participants were overweight. At this stage, androstenedione, testosterone, and estrogens were positively associated with %FGV but not AFGV. Two years post-menarche, no significant associations were observed. By 4 years post-menarche, progesterone was positively associated with %FGV. Mixed-effects models across showed positive associations between testosterone, androstenedione, progesterone, and DHEAS with both %FGV and AFGV in crude and adjusted models (Table 1). **Conclusions:** Our findings confirm positive associations between progesterone and androgenic hormones with %FGV and also with AFGV, particularly during puberty and adolescence. **Key Findings:** Sex hormones are significantly associated with %FGV and AFGV during critical periods of susceptibility, such as, puberty. **Impact on Screening Strategies:** Understanding the hormonal determinants of breast density during key life stages highlights the importance of integrating hormonal data into mammographic screening. Hormonal profiling could enhance personalized, risk-based screening approaches, improving early detection while reducing unnecessary imaging, particularly in resource-limited settings

Table N°1: Association between sex hormones and Breast Composition during and after puberty.

|                         | %FGV  |             |           |            | AFGV   |               |           |               |
|-------------------------|-------|-------------|-----------|------------|--------|---------------|-----------|---------------|
|                         | Crude |             | Adjusted* |            | Crude  |               | Adjusted* |               |
|                         | B     | 95%CI       | B         | 95%CI      | B      | 95%CI         | B         | 95%CI         |
| Estradiol (pg/mL)       | 0.003 | -0.02-0.02  | -0.00     | -0.02-0.01 | -0.24  | -0.35-(-0.13) | -0.24     | -0.35-(-0.12) |
| Androstenedione (ng/mL) | 3.79  | 2.31-5.28   | 3.09      | 1.80-4.37  | 46.07  | 34.94-57.20   | 43.83     | 32.68-54.98   |
| Testosterone (ng/mL)    | 17.72 | 10.75-24.68 | 13.53     | 7.63-19.42 | 152.87 | 101.51-204.23 | 147.36    | 96.17-198.55  |
| DHEAS (ng/mL)           | 0.002 | 0.00-0.00   | 0.00      | 0.00-0.00  | 0.04   | 0.03-0.04     | 0.04      | 0.03-0.04     |
| Progesterone (ng/mL)    | 4.33  | 2.53-6.13   | 2.69      | 1.12-4.25  | 35.166 | 21.44-48.89   | 36.50     | 22.70-50.30   |

\*Adjusted by: birth weight, maternal education level, BMI z-score, and age at menarche

## Communicating Breast Density and Breast Cancer Risk: Global Insights, Local Lessons, and the Consumer Voice

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**Introduction:** Breast density notification is increasingly recognized as a standard of care worldwide.<sup>1</sup> Dense breast tissue increases the risk of developing breast cancer and reduces mammographic sensitivity, potentially delaying detection. Communicating this information, in the broader context of breast cancer risk remains a challenge. **Objectives:** To examine global practices in breast density and breast cancer risk communication, share insights from the Australian experience, and highlight the role of social media advocacy in raising awareness and influencing change. **Methods:** A review of international literature on breast density notification and risk assessment, including an analysis of Australian research and initiatives was performed. Insights were drawn from health literacy studies, consumer communication preferences, and evidence supporting co-designed healthcare information resources. The impact of social media campaigns from consumer advocacy organizations was also explored. Personal lived experience with dense breasts and high breast cancer risk provides context for practical communication strategies. **Results:** Women often have limited understanding of breast density, its implications, and its role in breast cancer risk, hindering informed decision-making.<sup>2</sup> International guidelines emphasize transparency and shared decision-making. While consumer trust remains strong in healthcare professionals, the internet increasingly influences health behaviors. Australian research highlights the importance of culturally sensitive, multi-format communication, revisited at key points across the screening journey.<sup>2</sup> Co-designing resources with consumers improves relevance, clarity, and accessibility, addressing barriers for underserved populations, including those with low health literacy and diverse cultural backgrounds. **Conclusion:** Breast density notification presents an opportunity to enhance breast cancer risk awareness and empower women through personalized, empathetic, and culturally appropriate communication strategies. International collaboration, consumer partnership, and social media advocacy with curated content, may support local implementation to progress meaningful improvements in breast cancer screening outcomes. **Key finding:** A consumer-centered approach, supported by transparent communication, co-designed resources, and culturally sensitive strategies, can address gaps in breast density understanding and breast cancer risk awareness, empowering women to make informed decisions about their breast health. **Impact on screening strategies:** To translate these findings into practice, screening professionals can focus on creating clear, transparent conversations about breast density and breast cancer risk, assisting women to understand their screening outcomes and options. Co-designed educational resources and culturally tailored communication tools can be integrated into routine practice to address diverse literacy levels and cultural backgrounds. Social media platforms offer additional opportunities to reinforce key messages and reach underserved populations. Together, these strategies can enhance trust, engagement, and follow-through with recommended care pathways.

**Acknowledgements:** To be advised.

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## Comparative Analysis of Machine Learning Approaches for Breast Cancer Risk Prediction: Combining Breast Density, Polygenic Risk Scores, and Clinical Factors

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**Introduction:** Breast density is a well-established risk factor for breast cancer, the most common cancer among women in the United States aside from skin cancer. Higher breast density not only increases cancer risk but also reduces mammographic sensitivity, making both risk prediction and early detection more challenging. **Objective:** This study evaluates the predictive performance of multiple machine learning models that integrate breast density with polygenic risk scores (PRS) and other clinical factors. **Methods:** After testing several PRS models, we identified 313-SNP model from the PGS catalog as the best-performing genetic risk predictor. We compared three predictive models incorporating this PRS along with age, body mass index (BMI), five genetic principal components (PC1-5), and breast density as predictor variables. Logistic Regression (LR), Multilayer Perceptron (MLP), and Probabilistic Graphical Model (PGM) were implemented to assess breast cancer risk. MLPs are artificial neural networks that can detect non-linear relationships in data through layers of interconnected "neurons," while PGMs use Bayesian statistics to determine feature importance and correlation. **Results:** Among 3,000 African ancestry women from the Penn Medicine BioBank, Logistic Regression demonstrated the highest predictive accuracy at 0.69, followed by Probabilistic Graphical Model at 0.64 and Multilayer Perceptron at 0.63. Our study suggests limited interaction between PRS and clinical factors, including breast density, in breast cancer prediction. These findings align with prior research demonstrating the largely independent nature of polygenic risk scores from traditional clinical risk factors. **Conclusion:** These findings underscore the challenges in developing more sophisticated risk prediction models and highlight the need for alternative approaches to capture the complex genetic architecture of breast cancer risk. Our future research aims to enhance our risk assessment models by: (1) incorporating moderate and high penetrance genes, (2) testing novel PRS methods specifically designed for multi-ancestry populations, with a focus on African populations, (3) implementing more comprehensive risk factor data and quantitative breast density measures, and (4) investigating the potential mediating effect of breast density in breast cancer development. These additional components and analyses could improve our understanding of the relationship between genetic factors, breast density, and cancer risk, potentially leading to more precise risk stratification strategies.

**Key Findings:** Our analyses revealed limited interactions between PRS and clinical factors, including breast density. Notably, logistic regression outperformed more complex machine learning approaches.

**Impact on Screening Strategies:** Our findings suggest potential benefits of risk-stratified screening approaches that incorporate genetic and non-genetic risk factors in informing personalized screening intervals.

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## Investigating the impact of radiotherapy and endocrine therapy on mammographic breast density changes in the contralateral breast of breast cancer survivors

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**Background:** Among breast cancer survivors, contralateral breast cancer risk may increase with radiotherapy and decrease with endocrine therapy. Treatment-associated changes in mammographic breast density (MBD) may be a biomarker of adverse or beneficial treatment effects. Little is known about the influence of radiotherapy, alone or in combination with endocrine therapy, on MBD. We evaluated individual and joint effects of radiotherapy and endocrine therapy on MBD change within the contralateral breast among breast cancer survivors. **Methods:** Serial mammograms from 636 patients were retrieved from the Kaiser Permanente (KP) Breast Cancer Survivors Cohort (diagnosed at ages 35-84 years, in KP-CO or KP-WA, from 1990-2014) who underwent surgery for stage I-III disease and survived at least one year. Patients with a baseline (pre-diagnosis) mammogram and at least one follow-up (post-diagnosis) mammogram of the contralateral breast were included. Treatment data was collected from electronic medical records. Change in percent MBD ( $\Delta$ MBD, using Cumulus) from pre- to post-diagnosis was calculated by patient characteristics and treatments. Generalized linear models (adjusted for age at diagnosis, study site, BMI, and baseline MBD) were used to estimate least square mean  $\Delta$ MBD and 95% confidence intervals (CIs) by radiotherapy, endocrine therapy, and their combination. **Results:** The mean time between baseline and follow-up mammograms was 6.6 years (IQR: 3.1-9.1 years), with an average decrease in MBD of 8.4% (IQR: -14.4 to -1.0%). Factors associated with greater mean MBD decreases ( $p < 0.01$ ) included younger age, lower BMI, and higher MBD at diagnosis, as well as receipt of chemotherapy or tamoxifen only. MBD decreased 10-11% among those treated with Tamoxifen (alone or with radiotherapy, **Table 1**). Radiotherapy alone was not significantly associated with  $\Delta$ MBD. Patients who greater MBD decreases, regardless of whether they received tamoxifen only (adjusted  $\Delta$ MBD [95% CI] = -3.2 [-5.9, -0.5]), or combined tamoxifen and radiotherapy (-3.1 [-5.4, -0.8]), compared with those who did not receive tamoxifen or radiotherapy. Similar patterns were observed when restricting to ER-positive patients ( $n=494$ ).

**Conclusions:** Tamoxifen-associated decreases in MBD were not affected by radiotherapy receipt in this population of breast cancer survivors. Future work will assess how associations between breast cancer treatment and contralateral breast cancer risk may be mediated by  $\Delta$ MBD. **Key finding:** Tamoxifen was associated with decreased MBD, even when combined with radiotherapy. **Impact on screening strategies:** Patient characteristics and breast cancer treatments may differentially affect MBD changes, which in turn can impact mammographic sensitivity, an important consideration for surveillance among breast cancer survivors.

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**Table 1.** Absolute  $\Delta$ MBD of the contralateral breast from baseline to post-diagnostic mammogram, according to treatment modality

| Radiotherapy/Tamoxifen use | N (%)    | Mean  | IQR           |
|----------------------------|----------|-------|---------------|
| None                       | 68 (11)  | -7.6  | (-17.0, 0.7)  |
| Radiotherapy only          | 275 (44) | -6.1  | (-11.0, -0.1) |
| Tamoxifen only             | 78 (12)  | -11.9 | (-21.3, -3.6) |
| Both                       | 210 (33) | -10.6 | (-15.6, -3.0) |

IQR = interquartile range,  $\Delta$ MBD = change in percent mammographic breast density

received tamoxifen experienced

Improved Long-Term Breast Cancer Risk Prediction Through Analysis of Sequential Mammograms Leveraging State-of-the-art AI Model

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**Introduction:** Mammogram-based artificial intelligence (AI) models have demonstrated a promising role in breast cancer risk prediction. However, most AI models treat mammograms as isolated instances, when women at screening generally have a series of prior mammograms available. **Objectives:** We extend a state-of-the-art AI breast cancer risk model (MIRAI; MGH[1]) with the goal to leverage a woman's available history of mammograms in evaluating her long-term risk of developing breast cancer. **Methods:** Data were retrospectively analyzed from 8,385 individual women (64% White women; 36% Black women) who underwent at least three negative mammograms (Hologic Inc.) at Washington University in St. Louis, MO within 7 months to 10 years prior to their breast cancer diagnosis (N=1,098 breast cancer cases) or last negative screening (N=7,287 controls). We developed and evaluated a longitudinal AI model built upon the MIRAI encoder to extract features from the four views of each mammogram which are then ingested into a temporal module with a recurrent neural network to capture temporal changes across the three exams. We also compared our longitudinal AI model with: (1) single-exam AI analysis via a convolutional neural network (CNN) fed with the MIRAI encoder features from a woman's oldest (M3) or most recent (M1) mammogram; and (2) non-temporal, CNN-based, integration of MIRAI encoder features from all three mammographic exams (M1-M3). All evaluations were performed using ten repetitions of stratified hold-out splitting (80% training, 20% test). We report on the area under the receiver operating characteristic curve (AUC) and balanced accuracy (BAC) on the test set. **Results:** Our longitudinal AI model achieved AUC of 0.83 and BAC of 0.76 (Table 1). Its breast cancer risk prediction performance was significantly ( $p < 0.05$ ) superior to single-exam AI models which achieved AUCs of 0.77 (M3) and 0.78 (M1), and BAC of 0.70 (M3) and 0.72 (M1). Performance was also higher, yet not statistically significant, from the performance of non-temporal integration of the three exams (AUC = 0.82 and BAC = 0.75,  $p = 0.72$ ). **Conclusion:** Our preliminary results show that analyzing multiple prior mammographic exams significantly enhances long-term breast cancer risk prediction over single-exam predictions, with modeling of longitudinal associations potentially adding to further improvement. **Key Finding:** Leveraging the wealth of information contained in sequential mammograms improves long-term breast cancer risk prediction. **Impact on Screening:** Advancements in personalized breast cancer risk assessment may help reduce the number of cancers diagnosed at a later and more aggressive stage.

Table 1. Breast cancer risk prediction performance of mammogram-based AI models on test set.

| AI model                 | Input                      | AUC         | BAC         | SEN         | SPEC        | p      |
|--------------------------|----------------------------|-------------|-------------|-------------|-------------|--------|
| Single-exam analysis     | Most recent mammogram (M1) | 0.78 ± 0.01 | 0.72 ± 0.02 | 0.59 ± 0.04 | 0.84 ± 0.04 | < 0.05 |
|                          | Oldest mammogram (M3)      | 0.77 ± 0.01 | 0.70 ± 0.01 | 0.68 ± 0.04 | 0.73 ± 0.05 | < 0.05 |
| Non-temporal integration | Three prior mammograms     | 0.82 ± 0.01 | 0.75 ± 0.02 | 0.65 ± 0.06 | 0.85 ± 0.03 | 0.72   |
| Longitudinal analysis    | Three prior mammograms     | 0.83 ± 0.01 | 0.76 ± 0.01 | 0.67 ± 0.05 | 0.84 ± 0.04 | n/a    |

Note – all metrics include mean ± standard deviation. p: p-value for difference from longitudinal AI analysis via permutation tests.

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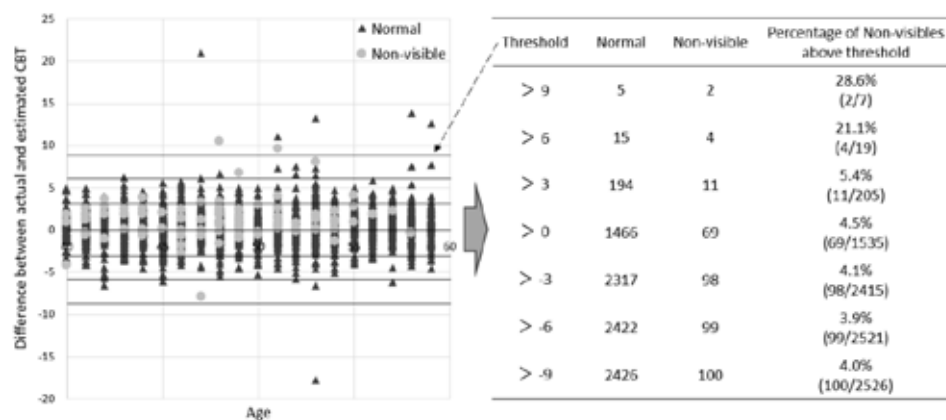
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## Breast Cancer Risk Assessment by Use of Estimated Compressed Breast Thickness from Mammogram

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**Introduction:** The amount of mammary glands on mammograms is associated with breast cancer and masking risk. Actually, there are cases in which the mammogram shows no or only benign findings, but cancer is detected on ultrasonography (non-visibles). Breast density is often used as a factor of breast cancer risk. However, it usually relies on subjective judgment, and physicians' variation is often a problem. We focused on compressed breast thickness (CBT), which can be measured mechanically. The dense breast has thinner CBT on mammograms<sup>(1)-(4)</sup>. If cancer is masked in the mammary glands, the mammary glands may be depicted as denser than normal. Therefore, the actual CBT could be expected to be thicker than the CBT guessed from the appearance. **Objectives:** By developing an Artificial Intelligence (AI) that can estimate CBT of normal with high accuracy, we hypothesized there would be a divergence between the estimated CBT of normal and non-visibles with the AI (estimated CBT would be smaller than actual CBT). This study aims to find factors that indicate non-visibles by using estimated CBT from mammograms. **Methods:** We used 26,226 normals and 150 non-visibles. Normals were separated into 18,229 for training, 4,142 for tuning, and 3,855 for testing. Non-visibles were used only for testing. We used ResNet18 model, squared error for the loss function, 0.001 for the learning rate, and 32 for the batch size. For the difference between actual and estimated CBT, we analyzed the divergence between normals and non-visibles. **Results:** The correlation coefficient between actual and estimated CBT for normal testing was highly accurate at 0.989. The average value of the difference between actual and estimated CBT by age group was statistically superior for non-visibles in the 40-50 years, and 21.1% of all cases with a difference of six or more between actual and estimated CBT are non-visibles (Figure 1). **Conclusion:** CBT could be estimated from mammograms with high accuracy using AI. The difference between actual and estimated CBT was statistically superior in non-visibles, suggesting the possibility of using this method for screening breast cancer. **Key finding:** In the 40-50 years, recommending additional tests such as ultrasonography with a difference of six or more between actual and estimated CBT may detect about 20% of cancer. **Impact on screening strategies:** If the trend of non-visibles can be determined from this result, it will be possible to select patients for combined mammography and ultrasonography, leading to early detection of cancer.



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## Performance of the Breast Cancer Surveillance Consortium (BCSC) risk model among breast cancer cases in Hawaii

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**Background:** Cancer risk models are an important tool for primary cancer prevention. The Breast Cancer Surveillance Consortium 5-year invasive cancer risk model is a widely used model that has been validated in a number of populations. However, little is known about its performance in the multiethnic population of women in Hawaii.

**Objectives:** We examined the 5-year invasive breast cancer risk estimated by BCSCv3 among 954 cases of the Hawaii and Pacific Islands Mammography Registry (HIPIMR), which contains information on women who completed mammograms at one of the 4 participating clinics between 2009 and 2019 prior to their breast cancer diagnosis.

**Methods:** We utilized age, race/ethnicity, BI-RADS breast density, history of breast biopsy, family history of breast cancer, age at first live birth, body-mass index (BMI) category and menopausal status to calculate the BCSCv3 5-year risk. Across all women and within the Asian, Native Hawaiian, and White groups we calculated the mean 5-year risk and the percentage classified as high-risk for screening (5-year risk  $\geq 1.67\%$ ) or chemoprevention (5-year risk  $\geq 3\%$ ) by categories of the risk factors.

**Results:** Overall, 38% of breast cancer cases were classified as risk  $\geq 1.67\%$  and 4.2% as  $\geq 3.0\%$ . The respective percentages were higher among Native Hawaiians (69.5% and 21.9%) and Whites (60% and 7.0%) and lower among Asian women (28.3% and 0.3%). Women of older age, postmenopausal, with family history of breast cancer or older age at first live birth were classified as  $\geq 1.67\%$ ; with proportions highest among Native Hawaiian and White women. A higher proportion of women with extremely dense breasts was classified as  $\geq 1.67\%$  or  $\geq 3.0\%$ , especially among Native Hawaiian women (100% and 50%, respectively). Women with obesity ( $30 \leq \text{BMI} < 35 \text{ kg/m}^2$ ) or extreme obesity ( $\text{BMI} \geq 35 \text{ kg/m}^2$ ) had a higher proportion classified as high risk. Fewer than 50% of Asian breast cancer cases were classified as  $\geq 1.67\%$  or  $\geq 3.0\%$  across all categories except those with  $\text{BMI} \geq 30$ .

**Conclusions and Key Findings:** The BCSCv3 model classified a high proportion of breast cancer cases as high-risk among Native Hawaii women but not among Asian women. Further research is needed to identify the causes of this difference and to evaluate BCSCv3 on a broader sample of Hawaii women.

**Impact on Screening Strategies:** The BCSCv3 could be evaluated within racial/ethnic groups in Hawaii to identify high risk women for prevention strategies.

## Modelling Breast Cancer Risk Using Health Records to Identify Women for Early Mammography

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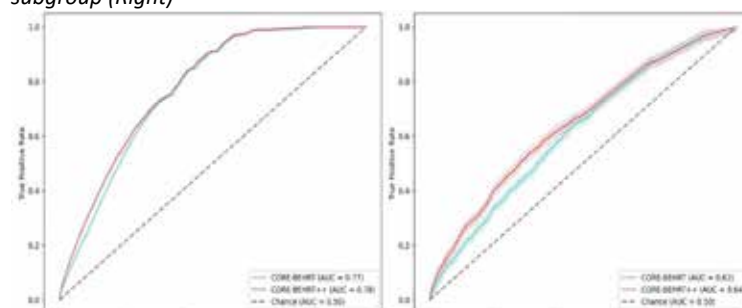
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**Background:** The U.S. Preventive Services Task Force recently lowered its recommended starting age for biennial screenings from 50 to 40. In Europe, screening age ranges vary and is in Denmark (50-69). Statistical models for personalised risk assessments such as the Gail model, the Tyrer-Cuzick model [1], Lauritzen's model [2], and the BOADICEA model [3] require patient information or imaging not readily available in the hospital system in terms of personal history, family history, mammography, or genetics. Obtaining this is impractical to scale across large populations of women only sparsely in contact with the healthcare system. Lately, there has been a trend in adapting machine learning architectures developed for natural language processing to Electronic Healthcare Records (EHR) data. Implementation of this mimics EHR codes as words, hospital visits as sentences, and healthcare histories as documents, adapting the BERT [7] architecture for this purpose, as demonstrated in the BEHRT [4], Med-BERT [5], and COREBEHRT [6]. **Methods:** Data was derived from the Eastern Danish region's EHR, including patients between 2016 and 2021. The model was tested in a simulated prospective setting using additional data from 2022 to 2024. We extracted medical events from the EHR. For each event, three key variables were extracted: the concept, the timestamp, and the admission ID. Diagnostic concepts were represented by ICD-10 codes, medications by Anatomical Therapeutic Chemical (ATC) codes, procedures by Classification of Surgical Procedures (NCSP) codes, and lab tests by their test names and test value. This training data consisted of a total of 811,230,774 codes. In this study, we adapted the COREBEHRT [10] methodology including diagnosis, administered in-hospital medications, to form the COREBEHRT++ also including procedures and laboratory test results to predict breast cancer risk. **Results:** The simulated prospective validation cohort included 1,055,666 patients, with 192,807 aged 40-50.

The COREBEHRT++ model achieved a ROC AUC of 0.78 in the simulated prospective testing. In the 40-50-year and +40-year subgroups, the ROC AUCs were 0.64 and 0.63, respectively. Especially injuries, but also musculoskeletal, endocrine and genitourinary diseases show importance for prediction of breast cancer.

**Key Finding:** The COREBEHRT++ model successfully identified a subset of 23.9% of 40-50-year-old women with an average breast cancer risk equal to or higher than that of the ordinary screening population comprised of women aged 50-69 in the development-validation group. **Impact on Screening strategies:** These results demonstrate a scalable tool using only readily available information for identifying high-risk individuals who may benefit from earlier mammography screening.

Table 5. AUC on the whole prospective cohort (Left) and on the 40-50y subgroup (Right)



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## Background fibroglandular uptake: A new parameter for breast tissue activity from dedicated breast PET

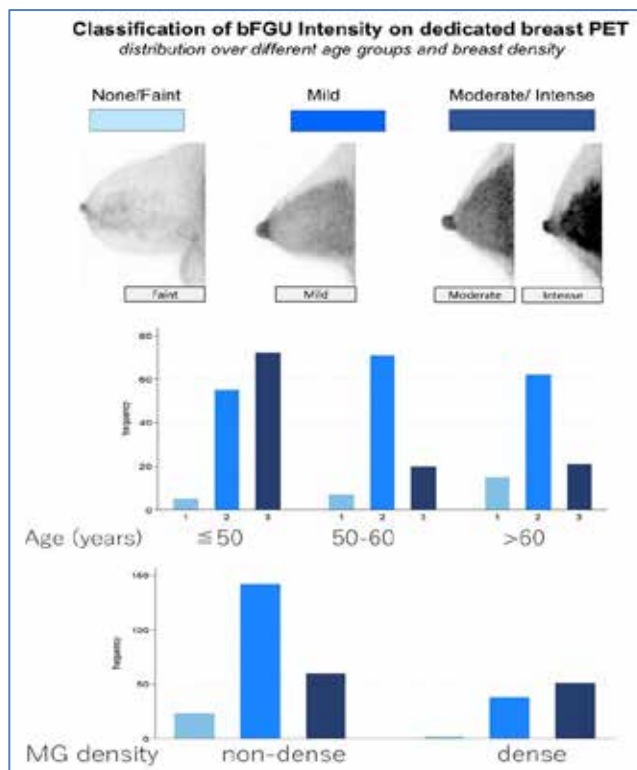
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**Introduction:** Dedicated breast (db) positron emission tomography (PET) is an organ-specific technique that provides detailed breast imaging with high spatial resolution. dbPET detects actively proliferating tissues via increased glucose metabolism, indicating that background uptake reflects the proliferative activities of fibroglandular tissues. We hypothesized that **background fibroglandular uptake (bFGU)** on dbPET could reflect breast tissue proliferation and serve as a new imaging marker for breast cancer risk, similar to breast density on mammography or background parenchymal enhancement on MRI. As a benchmark, we need to determine the distribution of bFGU among healthy women. **Objectives:** This study aimed to investigate the distribution of bFGU according to age and to identify the factors associated with bFGU among healthy women from opportunistic screening. **Methods:** Study population: Using a dataset of 328 participants who underwent dbPET at our screening center from January to September 2020, standardized dbPET reports were extracted. Age and visually assessed mammographic density were extracted from reports and electric medical records. Analysis: bFGU was recorded using a dedicated breast PET lexicon (1). bFGU was evaluated in amount and intensity, which was classified into "Faint," "Mild," "Moderate" and "Intense" (Figure1: top row). The deviation in

frequencies among categories was examined using the chi-square test. **Results:** A total of 326 women (mean age, 54, range 30-85 years) were included. For bFGU Intensity, the number of women classified as "Faint," "Mild," "Moderate" and "Intense" were 24, 188, 112, and 1 respectively. The frequencies of "Moderate/Intense" bFGU were 54 % for women under 40, while 20-21% for women over 40 (Figure1: mid row,  $p < 0.001$ ). For mammographic density, the frequencies of "Moderate/Intense" bFGU were 27% and 56% among women with non-dense and dense breasts, respectively (Figure1: bottom row,  $p < 0.001$ ).

**Conclusion:** bFGU was more intense among women aged < 50 years and those with dense breasts. **Key finding:** The distribution of bFGU among women in the screening population were associated with age and breast density. **Impact on screening strategies:** This is the first report describing the frequency of bFGU among the screening population, which can be used as a benchmark. The association of bFGU with future risk of breast cancer needs to be investigated.



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# Integrated Breast Density Assessment and Cancer Detection with AI in Mammographic Screening: A Retrospective Comparison of Diagnostic Performance with Radiologists Across Breast Density Categories

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**Introduction:** Image interpretation by AI on digital mammography (DM) images in breast cancer screening has shown promising results (1). Some evidence indicates consistent performance of AI across BI-RADS density groups (2), but BI-RADS are adhered with risk of inter-observer variation (3). Automatic density assessments can overcome these variations (4). **Objectives:** To evaluate breast cancer detection using AI-software and compare its diagnostic performance in screening with radiologists across density categories assessed by the same AI-software. **Method:** Screening examinations with DM from a double reading screening program in Malmö, Sweden, 2010-2015 were retrospectively analyzed with a deep learning-based AI-software (Transpara 2.0.0, Screenpoint Medical). The AI-software assigned a likelihood score of cancer and breast density category, at exam level, in concordance with the BI-RADS 5<sup>th</sup> edition categories. A cut-off score for recall was selected to match the specificity of the first reader. Sensitivity of AI, used as a stand-alone reader, was compared with the first reader across the density categories. Non-inferiority was concluded if the lower limit of the 95% confidence interval (CI) of the difference was greater than the pre-specified margin at 5 percentage points (pp). **Results:** In total 91 072 examinations were divided into density categories A (10.8%), B (42.2%), C (33.6%) and D (13.4%). The sensitivity of the AI-software was 69.2% (95% CI: 65.7-72.5), non-inferior compared to first reader 66.1% (95% CI: 62.5-69.6), at matched specificity of first reader at 96.4% (Table 1). Non-inferiority between the AI-software and first reader was concluded for breast density category B and C with difference of 2.9 pp (95% CI: -4.3-10.1) and 4.7 pp (95% CI: -3.4-12.9), but not category A or D (-4.8 pp (95% CI: -20.1-10.6 and 0.0 pp (95% CI: -13.2-13.2)). **Conclusion:** These results show the potential of using AI-software for integrated density assessment and cancer detection with non-inferiority shown for the whole group as well as for subgroups of BI-RADS B and C. Non-inferiority was not shown for BI-RADS A and D, potentially due to fewer individuals. **Key finding:** An AI-software showed an overall diagnostic performance non-inferior compared with the first reading radiologist in a double reading program, likely independent of breast density category. **Impact on screening strategies:** These results add evidence to the potential of changing the European reading practice with two radiologists into single reading + AI. Also, the integrated density assessment could be used in future risk-based screening approaches.

Table 1. Sensitivity with differences between Transpara and first reader with 95% confidence intervals (CI). Matched specificity of Transpara and first reader. Stratification by BI-RADS density. \*non-inferior

|           | Number of exams (%) | Sensitivity Transpara (95% CI) | Sensitivity First Reader (95% CI) | Matched Specificity | Difference (95% CI) |
|-----------|---------------------|--------------------------------|-----------------------------------|---------------------|---------------------|
| All women | 91 072 (100%)       | 69.2% (65.7-72.5)              | 66.1% (62.5-69.6)                 | 96.4%               | 3.1% (-1.8-7.9)*    |
| BI-RADS A | 9 824 (10.8%)       | 71.4% (58.7-82.1)              | 76.2% (63.8-86.0)                 | 98.1%               | -4.8% (-20.1-10.6)  |
| BI-RADS B | 38 406 (42.2%)      | 76.9% (71.5-81.8)              | 74.0% (68.4-79.1)                 | 96.9%               | 2.9% (-4.3-10.1)*   |
| BI-RADS C | 30 620 (33.6%)      | 63.3% (57.3-69.0)              | 58.5% (52.5-64.4)                 | 95.8%               | 4.7% (-3.4-12.9)*   |
| BI-RADS D | 12 222 (13.4%)      | 59.4% (49.5-68.9)              | 59.4% (49.5-68.9)                 | 95.1%               | 0.0% (-13.2-13.2)   |

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## Genome-Wide Association Meta-Analysis Identifies Novel Genetic Loci Associated with Breast Density Phenotypes

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**Introduction:** Breast density phenotypes, including dense tissue area or volume (DA), non-dense tissue area or volume (NDA), and percent density or volume (PD), are associated with breast cancer risk. While these traits are highly heritable, the genetic susceptibility loci identified thus far explain only a portion of the estimated heritability for DA, NDA, and PD. **Objectives:** We aimed to evaluate genetic factors associated with breast density phenotypes in adult women, including a focus on premenopausal women. **Methods:** We conducted a genome-wide association study (GWAS) meta-analysis of age- and BMI-adjusted density traits in up to 36,334 women of European genetic ancestry from the Breast Cancer Association Consortium (BCAC, N=27,900) and the Mayo Clinic Biobank (N=8,434). Additionally, we focused analyses on up to 10,104 premenopausal women of European genetic ancestry from BCAC (N=7,120), Mayo Clinic Biobank (N=2,133), and the Young Women study (N=851). **Results:** We identified 14 novel loci associated with DA, NDA, or PD at a genome-wide significance level of  $5 \times 10^{-8}$  (DA: 1q24.2, 6p21.31, 7p22.2, 10p12.1, 17q24.3, 18q12.1, 19q13.43; NDA: 4q24, 6p21.1, 10q25.3; and PD: 2q12.1, 5q15, 6p21.1, 6p21.31, 7p22.2, 8q24.12, 10q25.3, 12q21.2). For premenopausal women, we observed a novel association between PD and a variant intronic to the *SETBP1* gene (18q12.3;  $p = 2.9 \times 10^{-8}$ ), which has been previously reported to be associated with breast cancer. Additional susceptibility loci identified in premenopausal women (DA: 4q13.3, 5q23.2, 10q21.2, 19q13.33, 22q13.2; NDA: 8p11.23; and PD: 10q21.2) overlapped with previously known density-associated loci. **Conclusion:** This study identified several novel genetic loci associated with breast density, including a novel locus specific to premenopausal women in a gene that has been reported to be associated with breast cancer risk. **Key finding:** These findings provide new insights into the genetic component of breast density phenotypes. **Impact on screening strategies:** A deeper understanding of breast density genetics, including for women in premenopausal years, may elucidate the role of density phenotypes in breast cancer risk and may improve the precision of polygenic risk scores designed to inform breast cancer screening strategies.

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## Utilization of polygenic-integrated risk assessments is higher in women with dense breast tissue or family history.

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**Introduction:** Breast density notification allows for the communication of risk to patients; however it leaves clinicians having to deal with ambiguity regarding subsequent clinical action. Risk assessment provide absolute risk scores to guide screening and risk reducing recommendations in the context of breast density. **Objectives:** We identified a trend of clinical characteristics for 376 women who had previously had a mammogram in the United States or Australia on whom PRS-integrated risk assessments were ordered in a commercial setting.

**Methods:** The commercially available PRS-integrated risk model was physician-ordered on US (n=266) and Australian (n=110) healthy, asymptomatic women above 30. The CLIA-certified, NATA accredited lab report defines increased risk by lifetime risk scores greater than 20% or 5-year risk scores greater than 1.67% for US women and greater than 25% lifetime for Australian women.

**Results:** The average patient age was 52 +/- 10 years. 78% of the women identified as White, 13% Asian, 3% Black, 5% Hispanic and 1% Native American or Pacific Islander. 48% of the women had no 1<sup>st</sup> or 2<sup>nd</sup> degree family history of breast cancer, with 11% having both 1<sup>st</sup> and 2<sup>nd</sup> degree family history, and 14% having 1<sup>st</sup> only and 26% having 2<sup>nd</sup> only. 32% of women were identified at-increased risk of breast cancer with a mean lifetime risk of 28%+/-16%. Excluding the 32% (n=120) of women that did not know their breast density status, 74% of the remaining 256 women had heterogeneously or extremely dense tissue.

**Conclusion:** Absolute risk scores were stratified across all four BIRADS categories underscoring the importance of applying risk assessment in the context of breast density status to get a more comprehensive picture of risk.

**Key finding:** The patient population risk-assessed was more likely to have dense breast tissue and some family history of breast cancer compared to normal population distributions of both risk factors. **Impact on screening strategies:** Clinicians were more likely to order a PRS-integrated risk score for a patient that had a risk factor such as family history or breast density suggesting the providers are looking for alternative screening options for their patients who are sitting close to a threshold of risk utilizing a traditional clinical model. Decision-making discussions around supplemental screening and risk-reduction options were available to a third of the patients assessed based on their lifetime risk scores over an actionable threshold.

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## Liquid biopsy-based assessment of a multimodal platform for early detection in breast cancer patients

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**Introduction:** Women with dense breast tissue face a two-fold higher risk of breast cancer<sup>1-2</sup>, yet mammography is less effective in this group, underscoring the need for more sensitive and accessible screening methods<sup>3-6</sup>. Emerging evidence indicates that cancer cells disseminate into blood vessels early in breast cancer, posing risks but also providing opportunities for detection and personalized interventions<sup>7-12</sup>. **Objectives:** This study evaluates the presence of early disease using a label-free multimodal approach combining cell and cell-free assays in women newly diagnosed with early-stage breast cancer (Stages 0-2). **Methods:** Blood samples from 125 Stage 0-2 treatment naive breast cancer patients and 145 healthy controls were collected. Samples were analyzed by Astrin Biosciences' AI-empowered proprietary label-free holographic imaging platform combined with in-flow protein marker expression for the presence of CTCs. The plasma was analyzed in parallel using a novel deep proteomic approach using label-free quantitative mass spectrometry. **Results:** Combined holography and immunofluorescent staining using PanCK+ and CD45/CD16- was used to validate enriched CTCs from early-stage breast cancer patients compared to healthy controls. The morphological features of individual cells from each patient clustered uniquely based on cell type as CTCs were more similar to breast cancer cell lines than to immune cells or other cancer cell lines (e.g. lung, colorectal, uterine). Deep proteomic profiling revealed differentially expressed proteins and oncogenic pathways (e.g. KRAS-Breast, EMT, etc.) in early-stage breast cancer from healthy patient controls, independent of breast density. **Conclusion:** We have developed a highly sensitive multimodal blood-based test that combines ultradeep proteomic profiling with cellular imaging using digital holographic microscopy to establish signatures in women who are undergoing screening for breast cancer. **Key finding:** This work enables Astrin Biosciences to develop a multimodal assay consisting of label-free holographic cellular imaging plus protein characterization of plasma for early detection of breast cancer, enhancing clinical diagnostics for early detection and therapeutic interventions. **Impact on screening strategies:** The assay advances clinical diagnostics by identifying proteomic and cellular markers for early detection of breast cancer, independent of breast density, while also highlighting women at risk for metastases. This innovative approach enables more precise therapeutic interventions and enhances screening strategies for high-risk populations.

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## Mendelian Randomization Analysis of Circulating Inflammatory Markers and Mammographic Density Phenotypes

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**Introduction:** Observational studies have identified associations between circulating inflammatory markers (CIMs), including IL-6, IL-8, TNFR2, VEGF, and C-reactive protein (CRP), and mammographic density (MD) phenotypes, such as dense area (DA), non-dense area (NDA), and percent density (PD). However, associations have varied across studies and traditional observational designs are subject to methodological limitations such as reverse causation and uncontrolled confounding. **Objectives:** We utilized a Mendelian randomization (MR) approach to assess potential causal relationships between CIMs and MD phenotypes. **Methods:** Using publicly available genome-wide association study (GWAS) data from individuals of European ancestry, we evaluated associations between genetically predicted IL-6, IL-8, TNFR2, VEGF, and CRP levels and MD phenotypes (DA:  $N = 11,636$ ; NDA:  $N = 11,707$ ; PD:  $N = 15,552$ ). To account for potential confounding by BMI, we also conducted a multivariable MR (MVMR) analysis incorporating genetic instruments for both BMI and CRP. **Results:** In univariate MR analyses, higher genetically predicted CRP levels were associated with modest increases in PD (0.197 sqrt(%) per 1 ln(mg/l) difference in CRP; 95% CI: 0.084,0.311;  $P = 0.0007$ ) and DA (0.169 sqrt(cm<sup>2</sup>) per 1 ln(mg/l) increase in CRP; 95% CI: 0.003,0.335;  $P = 0.046$ ). In MVMR analyses including genetically predicted BMI, we observed substantially attenuated associations between CRP levels and PD (0.093 sqrt(% density) per 1 ln(mg/l) difference in CRP; 95% CI: -0.013,0.198;  $P = 0.085$ ) and DA (0.84 sqrt(cm<sup>2</sup>) per 1 ln(mg/l) difference in CRP; 95% CI: -0.081,0.248;  $P = 0.32$ ). Genetically predicted CRP was not associated with NDA in either the MR or MVMR analyses. We did not identify associations between genetically predicted levels of IL-6, IL-8, TNFR2, VEGF and any MD phenotypes. **Conclusions:** These findings suggest that the observed associations between CIMs and MD phenotypes in previous observational studies may not reflect causal effects. **Key finding:** Previously observed associations between CIMs and MD phenotypes may not represent causal effects of CIMs on MD. **Impact on screening strategies:** The results suggest that CIM levels may not directly influence MD and may not be relevant factors when considering MD in breast cancer screening strategies.

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## Perceived Versus Actual Risk of Breast Cancer among Diverse, Community-Dwelling Women 18 to 50 Years of Age.

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**Introduction:** Leading guideline organizations and legislative mandates recommend assessing and informing women of their breast cancer (BC) risk.<sup>1</sup> Accurate understanding of one's BC risk is central to risk-based screening and may influence future screening behaviors, but women often misperceive their BC risk.<sup>2-3</sup> As efforts to implement risk-based approaches increase, more studies are needed to understand accuracy of risk, particularly among populations most susceptible to disparities. **Objectives:** This cross-sectional study characterizes accuracy of BC risk and examines differences in accuracy by personal characteristics among community-dwelling Hispanic and Black women between 18-50 years of age. **Methods:** Between March 2023 and June 2024, we recruited community-dwelling women self-identifying as Hispanic or Black, between the ages of 18 and 50, with no known BC gene mutations or personal diagnosis of BC (N= 277, 53% < age 40, 44% Spanish-speaking, 69% Hispanic, 31% Black) to complete a survey. Accuracy was the primary outcome and calculated as self-reported lifetime risk minus the Gail model lifetime risk and categorized as underestimated (perceived < 10% actual), accurate (perceived within 10% of actual), and overestimated (perceived > 10% of actual risk). Chi-square tests examined differences in accuracy by participant characteristics including race/ethnicity (Black vs. Hispanic), age (< 40 vs. 40+), language (English vs. Spanish), family history, and reproductive history. **Results:** Only 36% accurately estimated their BC risk with no significant differences observed by race/ethnicity, age, or language. Women with family history of BC overestimated their risk at significantly higher rates (79% vs 45%,  $p < 0.01$ ) compared to those without a family history. Women who had given birth accurately estimated their BC risk at higher rates (37% vs. 28%,  $p = .01$ ) and underestimated their risk at lower rates (5% vs 17%,  $p = .01$ ) compared to those who had never given birth. **Conclusion:** Diverse, community-dwelling women in our study tended to overestimate their BC risk with differences observed by family history and reproductive health. These findings underscore the need for targeted strategies to improve accuracy of BC risk. **Key Finding and New Insights Since 2023:** This study adds to the growing empirical evidence around accuracy of risk perceptions from diverse, community-dwelling women who may or may not be age-eligible for BC screening. **Impact on Screening Strategies:** Broad efforts are needed to improve accuracy of risk perceptions, particularly among populations susceptible to disparities in BC screening and outcomes and could promote uptake of appropriate risk reduction strategies among those at highest risk.

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Assessing breast cancer risk using an AI model combining lesion detection and mammographic texture

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**Introduction:** Risk-based mammography screening may improve earlier detection of breast cancer over standard screening by identifying high-risk women. A recent mammography-based risk model combined an AI detection model and mammographic texture to identify screen-negative high-risk women<sup>1</sup>. **Objectives:** This study retrospectively validated the risk model, and each of its input components, in two independent samples (public US database and a Danish cohort) in terms of risk segregation and how many future cancers were in the highest risk deciles. **Methods:** The Danish sample consisted of 50-70 year old women consecutively screened on Siemens systems from January 2016 to December 2017 with up to six years follow-up. The US database (EMBED) consisted of 40-74 year old women screened on Hologic systems in five US sites from July 2012 to February 2021<sup>2</sup>. The AI detection model generated exam scores, indicating probability of cancer. The texture model generated long-term risk scores. The full risk model combined the exam score, texture score, and volumetric breast density (VBD) to a five-year risk score. Risk assessments were evaluated for screen-negative women (cancer-free for 180 days). The AUCs of the input components were compared to full risk model using the DeLong test. **Results:** The Danish sample comprised 49,137 women with 872 breast cancers within six years. The US database comprised 15,820 women with 128 breast cancer within seven years. In the Danish sample, the AUCs were 0.70 for the AI detection model, 0.67 for the texture model, 0.56 for VBD, and 0.74 for the full risk model. In the US database, the AUCs were 0.66 for the AI detection model, 0.64 for the texture model, 0.52 for VBD, and 0.74 for the full risk model. In both samples, the full risk model AUC was significantly higher than each of the input components ( $P<0.001$ ). Of future cancers, 37% and 34% were in the highest risk decile in the Danish sample and in the US database, respectively. **Conclusion:** An AI-based breast cancer risk model integrating detection, texture, and density demonstrated improved risk assessment compared to individual input components across two independent datasets. **Key finding:** The risk model achieved an AUC of 0.74 in both datasets, with the highest decile accounting for 34%-37% of future breast cancers. **Impact on screening strategies:** This model offers identification of screen-negative women with elevated risk eligible for supplemental imaging which may improve early detection.

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Table 6. AUCs for different risk components and the full risk model

| Table 1: AUCs for different risk models |                           |                         |
|-----------------------------------------|---------------------------|-------------------------|
| Model                                   | Danish sample<br>(95% CI) | US database<br>(95% CI) |
| Detection                               | 0.70 (0.68, 0.72)         | 0.66 (0.62, 0.71)       |
| Texture                                 | 0.67 (0.65, 0.69)         | 0.64 (0.60, 0.69)       |
| VBD                                     | 0.56 (0.54, 0.58)         | 0.52 (0.47, 0.57)       |
| Full 5-year risk                        | 0.74 (0.72, 0.75)         | 0.74 (0.70, 0.78)       |

## Performance of Clinical Breast Cancer Risk Prediction Models Versus a Mammography-Based AI Risk Model

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**Introduction:** Clinical breast cancer (BC) risk prediction models show modest discriminatory accuracy. Deep learning of mammograms has resulted in artificial intelligence (AI) based models for BC risk with improved discriminatory accuracy relative to clinical models. However, there is little data on their calibration and agreement with clinical models. **Objectives:** We compared discriminatory accuracy, calibration and agreement of risk estimates for clinical BC risk prediction models (Gail, BC Surveillance Consortium v3 (BCSC) and Tyrer-Cuzick v8 (TC)) to the MIRAI AI-based risk prediction model. **Methods:** We utilized a cohort of 12,308 women from the Mayo Clinic Biobank who had screening digital mammograms and were followed for a median of 11.1 years (IQR: 4.2), with 250 incident BCs (176 invasive) occurring within five years. We assessed predicted *five-year* BC risk at enrollment using each model and estimated discrimination of both overall and invasive BC by the concordance (C) index and calibration by the observed to expected event ratio (O/E). We classified each model into high (top 20%) and moderate/low (bottom 80%) risk and evaluated agreement using weighted kappa (K) statistics. **Results:** MIRAI demonstrated greater discriminatory accuracy of invasive BC (C-Index: 0.72, 95% CI: 0.68, 0.75) compared to Gail (C-Index: 0.59, 95% CI: 0.55, 0.63) and BCSC (C-Index: 0.65, 95% CI: 0.61, 0.69).

Among women with TC score information (n=10,123), MIRAI demonstrated higher discriminatory accuracy for invasive BC (C-Index: 0.71, 95% CI: 0.67, 0.75) compared to TC with BI-RADS density (C-Index: 0.65, 95% CI: 0.61, 0.70).

| Model discrimination and calibration for prediction of overall and invasive BC |                   |                   |                   |                   |
|--------------------------------------------------------------------------------|-------------------|-------------------|-------------------|-------------------|
|                                                                                | Overall BC        |                   | Invasive BC       |                   |
| Model                                                                          | C-Index (95% CI)  | O/E (95% CI)      | C-Index (95% CI)  | O/E (95% CI)      |
| <b>Full Sample (N=12,308)</b>                                                  |                   |                   |                   |                   |
| MIRAI                                                                          | 0.71 (0.68, 0.74) | 0.96 (0.85, 1.08) | 0.72 (0.68, 0.75) | 0.68 (0.58, 0.78) |
| Gail                                                                           | 0.58 (0.54, 0.61) | 1.22 (1.07, 1.38) | 0.59 (0.55, 0.63) | 0.86 (0.74, 0.99) |
| BCSC                                                                           | 0.64 (0.60, 0.67) | 1.38 (1.22, 1.56) | 0.65 (0.61, 0.69) | 0.98 (0.84, 1.13) |
| <b>Reduced Sample (N=10,123)</b>                                               |                   |                   |                   |                   |
| MIRAI                                                                          | 0.71 (0.68, 0.74) | 1.01 (0.88, 1.15) | 0.71 (0.67, 0.75) | 0.73 (0.62, 0.85) |
| TC + BI-RADS                                                                   | 0.64 (0.61, 0.68) | 1.36 (1.19, 1.55) | 0.65 (0.61, 0.70) | 0.99 (0.84, 1.15) |

Although MIRAI performed well for overall BC, it showed worse calibration for invasive BC (O/E: 0.68) compared to Gail (O/E: 0.86), BCSC (O/E: 0.98), and the best-performing of TC models (with BI-RADS, O/E: 0.99) (See Table). Specifically, MIRAI tended to overestimate risk of BC for low-risk women. Finally, agreement of MIRAI risk was low for all models; K= 0.11 (95% CI: 0.09, 0.13) with Gail, K= 0.25 (95% CI: 0.23, 0.27) with BCSC, and K= 0.14 (95% CI: 0.12, 0.17) with TC + BI-RADS. **Conclusion:** MIRAI demonstrated improved discriminatory accuracy for 5-year invasive BC risk compared to the clinical models but was not well-calibrated for invasive BC. **Key finding:** Models trained for overall BC may not show adequate performance for prediction of invasive BC, which is the target for most prevention strategies. **Impact on screening strategies:** Development of AI-based risk models needs to consider invasive BC and evaluate both discriminatory accuracy and calibration to ensure appropriate application.

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## Sensitivity of an image-based breast cancer risk model to image quality

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**Introduction:** Studies demonstrating improved discriminatory capability of AI-driven image-based breast cancer risk models over traditional approaches are likely to influence guidelines for high-risk screening<sup>1</sup>. Recent work highlighting changes in 3-year image-based risk scores suggests a component tracking early cancer and shows that risk scores can vary substantially over time, even among patients remaining disease-free<sup>2</sup>. A gap we aimed to address here is to characterize variability in scores to understand how to manage and communicate changes in image-based risk profiles over successive screening rounds. **Objective:** This study tests the sensitivity of an existing image-based risk model to mammography image quality parameters. **Methods:** A retrospective analysis was conducted using screening mammograms from the OPTIMAM database<sup>3</sup> for clients aged 47-73. Cases with repeated imaging due to technical deficiencies in breast positioning (TP) or image blur (TB) were selected. Mammogram characteristics including volumetric breast density, compression pressure, and positioning quality were assessed using Volpara Imaging Software (v3.4). The Mirai risk model<sup>4</sup> predicted breast cancer risk using 4-view mammograms. Risk scores were compared between original studies and those with poor quality views replaced by repeat.

**Results:** The study included

1617 TP cases with one (94%) or two views repeated and 656 TB cases, with 95% having

one or two views repeated. While the TP group's mean change in risk was not significant, 343 cases (22.5%) showed changes in 5-year risk exceeding 10% of the original estimate. After repeat, a small increase in mean 5-year risk (0.18; 95% CI 0.0010–0.0026) was found for TB. Using a 1.67% 5-year risk threshold, 130 TP cases (8.5%) changed risk categorization, with 63 moving to high-risk and 67 to low-risk. In the TB group, 70 cases (10.8%) changed risk category, with 60 moving to high-risk and 10 to low-risk. **Conclusion:** Image quality can significantly impact image-based risk scores for some patients. **Key finding:** When repeating imaging for quality, approximately 10% of cases can be expected to change risk categorization if a 5-year threshold of 1.67% is used. **Impact on screening strategies:** Guidelines and models may be best applied with multiple studies over time to differentiate changes in scores tracking early onset disease vs image quality variations.

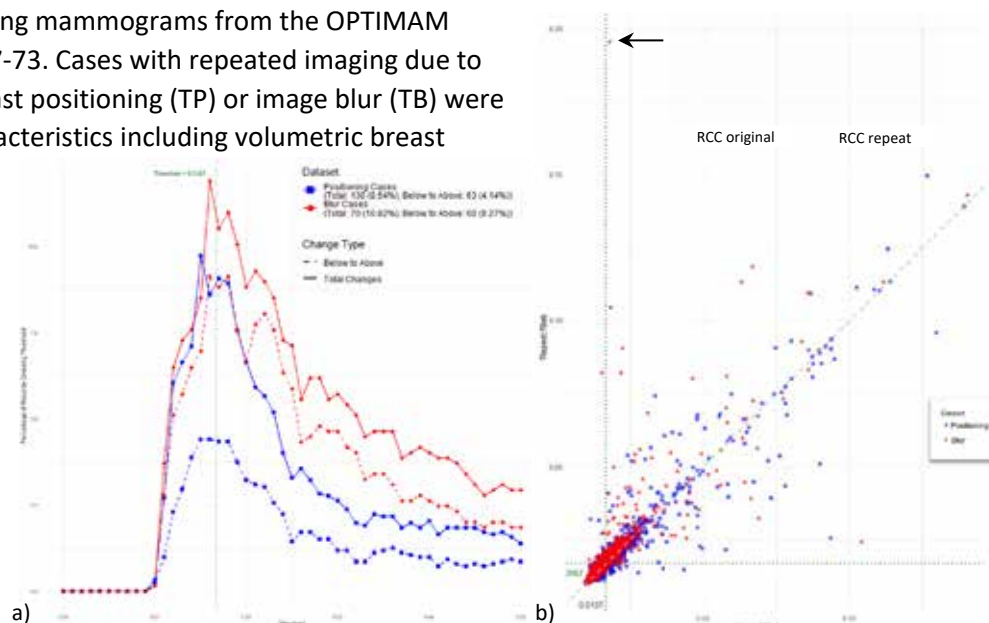


Figure 1. (a) Percentage of mammograms with change in 5-year image-based risk score after technical repeat per risk score threshold. (b) Scatter plot of predicted 5-year risk based on original mammograms (x-axis) vs exams with poor quality images replaced by repeated view(s) (y-axis). The inset illustrates the appearance of calcifications in a repeated vs original mammogram with blur.

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# The Interplay Between Breast Density and Acquisition Parameters on AI Performance in Screening Tomosynthesis

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**Introduction:** Technical parameters of tomosynthesis such as tube voltage (kVp) and current time product (mAs) have a known impact on human observer performance. However, the impact of these parameters on AI performance is not well known. We hypothesize that 1) tomosynthesis acquisition parameters impact performance of AI systems used in screening, and 2) breast density plays a role in determining how these parameters impact AI performance, beyond the impact on automatic exposure control (AEC). **Objectives:** Our overarching goal is to demonstrate that selection of breast-density specific acquisition parameters can yield improved AI performance. **Methods:** We retrospectively analyzed performance of a commercial AI breast cancer detection algorithm on 17,244 screening tomosynthesis exams from our institution, from January to September 2023 (Selenia Dimensions; Hologic Inc.). Subgroups were defined by quartiles of mAs and tertiles of kVp (equivalent to thickness tertiles for the AEC method used). To increase statistical power, initial ROC analysis was performed using BI-RADS 0 as ground truth. The kVp/mAs pairings which maximized area under the ROC curve in this analysis (AUC<sub>recall</sub>) were deemed “optimized” and subsequently compared to all other kVp/mAs settings combined (“non-optimized”) using pathology as ground truth (AUC<sub>path</sub>). Analyses were performed separately for “dense” (BI-RADS density C or D) versus “not-dense” breasts (BI-RADS density A or B). **Results:** For not-dense breasts, the 2<sup>nd</sup> quartile of mAs (58-70) led to optimized AI performance for all kVp values above 32 (AUC<sub>recall</sub> 0.76 vs 0.64). In dense breasts, mAs above 82 led to higher AI performance regardless of kVp (AUC<sub>recall</sub> 0.69 vs 0.60). These trends were consistent for AUC<sub>path</sub> (0.90 vs 0.84 in not-dense breasts and 0.94 vs 0.75 in dense breasts). All results except not-dense breast AUC<sub>path</sub> achieved statistical significance. **Conclusion:** Acquisition parameters impact AI performance differently depending on breast density. For not-dense breasts, reducing mAs may both decrease patient dose and improve AI performance in some patients. For dense breasts, higher mAs at any given kVp may improve AI performance. **Key finding:** Our preliminary data suggest that the acquisition protocol which optimizes AI performance may depend on a patient’s breast density, despite the use of AEC to maintain consistent detector exposure. The role of patient factors such as race or cancer subtype as potential confounders warrants additional study. **Impact on screening strategies:** Imaging protocols which are personalized to individual patients by incorporating demographic factors such as density may help to ensure consistent high performance of commercial AI algorithms.

Table 3. Impact of acquisition parameter optimization on ROC performance of commercial AI algorithm. AUC denotes area under the ROC curve. Recall denotes that BI-RADS 0 was used to determine ground truth for positive cases, path denotes that histopathology was used as ground truth. P-values were calculated via bootstrapping. Parentheses denote 95 percent confidence intervals.

| Breast Density | mAs/kVp       | AUC <sub>recall</sub> | p-value<br>recall | AUC <sub>path</sub> | p-value<br>path | N cases | N recalls | N cancers |
|----------------|---------------|-----------------------|-------------------|---------------------|-----------------|---------|-----------|-----------|
| Dense          | Optimized     | 0.69 (0.64,0.75)      | <0.005            | 0.94 (0.90,0.98)    | <0.005          | 804     | 104       | 6         |
|                | Not Optimized | 0.60 (0.57,0.63)      |                   | 0.75 (0.62,0.85)    |                 | 3520    | 446       | 21        |
| Not Dense      | Optimized     | 0.76 (0.70,0.81)      | <0.0005           | 0.90 (0.81,0.96)    | 0.19            | 1072    | 84        | 13        |
|                | Not Optimized | 0.64 (0.62,0.67)      |                   | 0.84 (0.78,0.89)    |                 | 4229    | 479       | 33        |

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## Analyzing Fairness of AI-driven breast cancer risk predictors and a Novel Interpretable Risk Predictor

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**Introduction:** AI methods significantly improve breast cancer risk prediction from screening mammograms. However, no prior work systematically studies the fairness of these models across critical patient attributes such as age, breast density, and BI-RADS categories. Existing risk predictors also lack interpretability, which hinders clinical adoption. To address these gaps, we (1) evaluate performance disparities in MIRAI [1], a state-of-the-art risk predictor, and (2) develop a novel interpretable risk predictor using multimodal learning. **Objectives:** 1. Evaluate MIRAI's performance stratified by age (<50, 50–70, ≥70), breast density (A/B vs. C/D), and BI-RADS (4 vs. 5); 2. Combine Mammo-CLIP [2] with a transformer to preserve MIRAI's predictive power while enabling enhanced interpretability through vision-language alignment. **Methods:** We use 10,033 anonymized patients (13,857 screening mammograms, 55,428 images) and use MIRAI as the baseline risk predictor. To evaluate fairness, we measure False Negative Rate (FNR) across different patient subgroups. For the interpretable model, we process each of the four standard mammographic views through Mammo-CLIP, generating semantically aligned embeddings. A transformer network integrates the image embeddings to predict the risk of cancer, leveraging knowledge distillation to align the student model closely with MIRAI's risks. **Results:** For 1 year risk (Figure 1a (top)), BI-RADS 5 exams demonstrate low FNR, indicating MIRAI accurately identifies overtly malignant findings, but higher FNR in dense breasts (C/D), younger patients (<50), and BI-RADS 4 highlights under-detection in these groups. Figure 1b (bottom) compares MIRAI's performance against the interpretable model over 1 to 5-year horizons. Two-sided p-values for differences in AUROC are <0.00001, confirming statistical significance. The new model's predictions correlate strongly with MIRAI's ( $r=0.70$ – $0.74$ ), demonstrating effective knowledge transfer without substantial loss of performance. **Conclusion:** Our analysis demonstrates that MIRAI exhibits performance disparities across critical attributes such as age, breast density, and BI-RADS categories, highlighting inherent biases in the model. The proposed interpretable risk predictor achieves comparable predictive performance while offering insights into decision-making through vision-language alignment. Future work will include additional sensitive attributes, such as race and demographics, and evaluating MIRAI's performance using a broader range of metrics, including AUROC and AUPRC across one-to-five-year horizons, to further analyze these disparities. **Key finding:** MIRAI exhibits performance disparities across age, breast density, and BI-RADS categories, indicating potential biases that could undermine equitable risk assessment. **Impact on screening strategies:** By identifying high-risk subgroups accurately and explaining model decisions, practitioners can tailor screening intervals and interventions, ultimately improving early detection and patient outcomes.

**References:** [1] Yala et al. Toward robust mammography-based models for breast cancer risk. *Science Translational Medicine* 13.578 (2021). [2] Ghosh et al. Mammo-CLIP: A vision language foundation model to enhance data efficiency and robustness in mammography. MICCAI 2024.

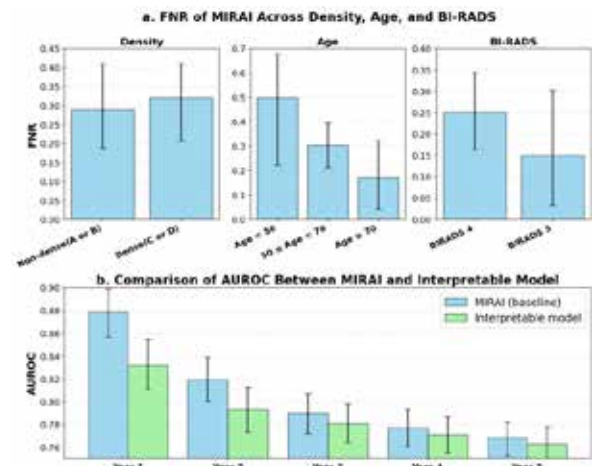


Figure 1: Quantitative analysis of our approach.

## Supervised Canonical Correlation Analysis Identifies Metabolite Super Pathways Associated with Mammographic Breast Density

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**Background:** Determining biomarkers of mammographic breast density (MBD) provides necessary insights into underlying biology and a guide towards those that can be targeted in breast cancer prevention. While a few metabolites have been associated with MBD, a broader and comprehensive approach investigating metabolites at the super pathway level is still lacking.

**Methods:** We enrolled 705 premenopausal women who provided blood draw during their annual screening mammogram at the Joanne Knight Breast Health Center at Washington University School of Medicine in St. Louis. We evaluated volumetric measures of MBD (volumetric percent density (VPD), dense volume (DV), and non-dense volume (NDV)) using Volpara (Volpara Health®). We performed untargeted metabolomic analyses at Metabolon (Durham, NC®). We performed supervised canonical correlation (CC) analysis (CCA) on each metabolite super pathway after standardizing each metabolite. Metabolites in each super pathway were represented by the first canonical correlation variate (CCA1) from CCA, to identify the super pathways most correlated with the MBD and subject to multiple linear regression with adjustment for confounders (age, race, body fat%, parity, age at first birth, family history of breast cancer, oral contraceptive use, alcohol intake, body shape at age 10). The Bonferroni and Benjamini-Hochberg false discovery procedure was applied to correct for multiple testing.

**Results:** We identified 828 metabolites from 10 super pathways: lipid I (n=217 metabolites), amino acid (n=211), xenobiotics (n=138), lipid II (n=54), peptide (n=43), nucleotide (n=38), cofactors and vitamins (n=37), carbohydrate energy (n=34), lipid III (n=34) and partially characterized molecules (n=22). We observed correlations between the 10 super pathways and VPD and NDV but not with DV. The strongest correlations were with 1) amino acid (CC= -0.73 with VPD and =0.81 with NDV); 2) lipid I (CC= 0.74 with VPD and =-0.80 with NDV); and 3) lipid II (CC= 0.6 with VPD and =-0.65 with NDV). Adjusting for confounders in multiple linear regression analyses identified amino acid and lipid I as the super pathways with the largest absolute coefficients, >0.15. The metabolites on the amino acid super pathway contributing to the CCA1 include hydroxyasparagine, 1-methylguanidine, N-acetylleucine, kynurenate, N-acetylalanine, and 2-hydroxy-3-methylvalerate which has a loading coefficient of absolute magnitude >0.25. Lipid I super pathway consists of fatty acid metabolites and lipid II consists of steroid hormone metabolites (mainly corticosteroids, androgenic, progestin and pregnenolone steroids).

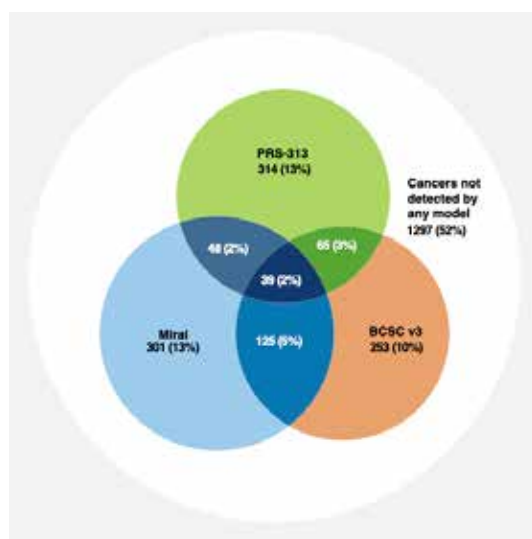
**Conclusions:** Using CCA, we observed that at the super pathway level, amino acids and lipids are most correlated with MBD. As expected, the directions of associations for all metabolite super pathways in relation to VPD were opposite to those observed for NDV.

## Comparative 10-year Performance of Mammography Artificial Intelligence, Clinical Breast Cancer Risk, and Polygenic Risk Models in the Kaiser Permanente Research Biobank

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*Figure 1. Relative overlap of cancers detected (i.e. sensitivity) for each individual breast cancer risk model when set at the top decile of risk threshold (i.e. >90% specificity) at 0-10 years.*



**Objectives:** To compare the relative performance of three domains of breast cancer risk models—the clinical risk model Breast Cancer Surveillance Consortium version 3 (BCSCv3), the polygenic risk model using 313 common variants (PRS313), and the mammography artificial intelligence algorithm Mirai—alone and in combination over 10-year time horizon. **Methods:** A prospective cohort was drawn from >400,000 patients enrolled in the Kaiser Permanente Research Biobank (KPRB) between 2003 and 2022. Women with a prior history of breast cancer or high-penetrant gene mutation were excluded. A negative screening mammogram (no clinically visible cancer) performed closest in time to KPRB enrollment defined the index date and was used to generate the Mirai algorithm risk score. KPRB patient survey and electronic health record data were used to generate the BCSC risk score. Saliva samples were genotyped and 313 common variants were used to generate PRS313, adjusted for genetic ancestry using eMERGE approach. Risk estimates for incident invasive breast cancer and DCIS 0 to 10 years after the negative mammogram were calculated after models were fit using a Cox model, with 5-fold cross validation used to estimate C-index. Combined model were created using linear combination of quantile normalized variables. **Results:** A total of 82,975 women were included, of whom 2,471 had incident cases. Approximately 75% were non-Hispanic White women.

The C-index (95% CI) for risk models at 0-1 year vs. 0-10 years were as follows:

BCSCv3 0.64 (0.59, 0.69) vs. 0.62 (0.60, 0.63); PRS313 0.61 (0.55, 0.66) vs. 0.61 (0.60, 0.62); Mirai 0.71 (0.66, 0.76) vs. 0.66 (0.65, 0.67); and combined BCSCv3, PRS313, and Mirai was 0.74 (0.70, 0.78) vs. 0.70 (0.69, 0.71). When using the top decile of risk at 0-10 years, BCSCv3 identified 19% cases (95% 17%, 20%) while a combined model of BCSCv3, PRS313, and Mirai identified 26% of cases (95% CI 24%, 28%). **Conclusion:** As compared to a breast cancer clinical risk model BCSCv3 and polygenic risk model PRS313, the mammographic AI model Mirai had significantly higher discrimination in the first year, which diminished but remained similar to BCSCv3 and PRS313 by year 10. The combined risk model did not improve discrimination above Mirai alone in the first year, but significantly improved performance over longer time horizons. **Key finding:** Breast cancer risk model domains are relatively independent in cancers identified at the higher and lower percentiles. **Impact on screening strategies:** A mammographic AI model best optimizes short term decisions for screening frequency and supplementary imaging, whereas a combined model best optimizes for longer term decisions such as primary preventative therapy.

**Acknowledgements:** This study was funded by National Cancer Institute R01CA264987, P01CA281826, and by The Permanente Medical Group Delivery Science and Applied Research. Data used in this study were provided by the Kaiser Permanente Research Bank (KPRB) from the KPRB collection, which includes the Kaiser Permanente Research Program on Genes, Environment, and Health (RPGEH). Access to data used in this study may be obtained by application to the KPRB at [kp.org/researchbank/researchers](http://kp.org/researchbank/researchers). We thank the participating women, mammography facilities, and radiologists for the data they have provided for this work.

## Testing validity of FFDM-based density evaluating AI algorithm for Synthetic Mammograms

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**Introduction:** Digital Breast Tomosynthesis (DBT) is the current standard screening method in the US. Its synthetic version, C-view, was developed to replace Full-field Digital Mammogram (FFDM). However, their image quality has been known to differ; for instance, C-view tends to emphasize lesion-like features (1). We previously developed an AI-based breast density evaluation algorithm (2) from 2D FFDM mammograms. The performance of our algorithm on C-view is uncertain, as it is new to our AI algorithm and could introduce potential errors.

**Objectives:** This study aims to test the validity of our FFDM-based density evaluating AI algorithm on C-view images reconstructed from DBT images.

**Methods:** Under the IRB-approved protocol, we curated 226 asymptomatic women (screening BIRADS 1 or 2, clinical density BIRADS A to D) whose FFDM and DBT were acquired simultaneously. For both image types, we used the “for presentation” version. We then applied our FFDM-based AI algorithm on both FFDM and C-view mammography reconstructed from DBT. To measure breast density, we computed the breast percent density (PD), which represents the ratio of dense area to the breast area. We also computed Average PD (APD) from four standard views (L/R-CC and L/R-MLO) for both FFDMs and C-view mammograms. We evaluated agreement between the density levels computed from FFDMs and C-view mammograms using the proportion of agreement within 0.05 as well as graphical tools such as Bland-Altman plot.

**Results:** The APD estimates demonstrate a high level of agreement between the traditional and synthetic images with the proportion of agreement within 0.05 of 89% (CI:84-93%) with the Bland-Altman limits of agreement from -0.06 to 0.06 (Fig. 1).

**Conclusion:** Without any finetuning on C-view images, our FFDM-based breast density AI algorithm can segment breast-dense tissue and reliably estimate percent density from a C-view.

**Key finding:** Although the image quality of C-view and FFDM may be different, our FFDM-based density AI algorithm can be used on C-view without any fine-tuning or adjustments.

**Impact on screening strategies:** This study shows that our FFDM-based density AI algorithm can reliably estimate the breast density from C-view from DBT. Breast density is one of the key risk factors of breast cancer, but there are limited algorithms available that can estimate breast density from “for presentation” versions of FFDM and C-Views from DBT. As our AI-based breast density algorithm works on C-views as well, it could facilitate the breast density assessment process for DBT images.

**Acknowledgements:** This work was supported in part by the National Institute of Health under Grant R37-CA248207.

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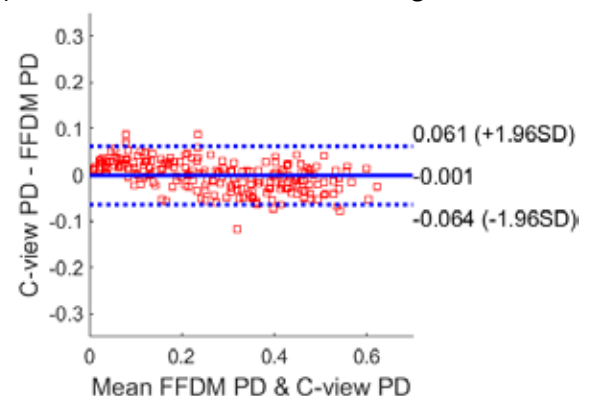


Figure 1. Agreement between APD estimates on FFDMs and corresponding C-view images by Bland-Altman plot.

## Utilizing Changes in Mammographic Breast Density Metrics for Enhanced Breast Cancer Risk Prediction

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**Introduction:** Incorporating a single mammographic breast density (MBD) measure into breast cancer risk models has been shown to increase the discriminatory accuracy of prediction models. However, MBD changes over time, and the predictive value of MBD changes remains unclear.

**Objectives:** We assessed the largest change in MBD ( $\Delta$ -MBD) between any two mammograms for an individual and evaluated its predictive performance alone and in combination with the Breast Cancer Risk Assessment Tool (BCRAT) risk score and a single MBD measurement.

**Methods:** We used Cumulus-assessed MBD data, expressed in percent density (PD) and dense area, from the IMAGES study, a nested case-control study (319 cases and 891 non-cases) within the Sister Study. We examined the discriminative power of adding  $\Delta$ -MBD (later-earlier MBD) with models containing single MBD (earlier or later mammogram of the pair with the largest MBD change) and/or the BCRAT risk scores ("combined model") by comparing the areas under the curve (AUC) of multivariable logistic regression models using the DeLong test. We analyzed relative and absolute  $\Delta$ -MBD, both continuously and categorically (decrease, stable, or increase). We stratified by age at earlier mammogram and menopausal status to better understand prediction accuracy among these groups.

**Results:** The combined models in the overall sample (e.g., AUC=0.64 (0.61-0.68) for model with categorical relative  $\Delta$ -MBD for PD, earlier mammogram, and BCRAT) performed marginally better (p-value = 0.0008) than BCRAT alone (AUC =0.57(0.53 - 0.61)). The contribution of  $\Delta$ -MBD beyond a single MBD was minimal (p-value = 0.09) when using either earlier or later mammogram MBD (e.g., AUC=0.63 (0.59 – 0.66) for model with earlier mammogram and BCRAT). Categorical  $\Delta$ -MBD had higher discrimination than continuous  $\Delta$ -MBD (e.g., AUC=0.58(0.54 - 0.61) vs AUC = 0.52(0.49 - 0.56) for models with only relative  $\Delta$ -MBD for PD). In the stratified analysis, combined models had higher AUCs in pre- vs post-menopausal women (e.g., AUC=0.69 (0.64-0.74) vs. AUC=0.62 (0.57-0.67) for models with categorical relative  $\Delta$ -MBD for PD, earlier mammogram, and BCRAT), and younger vs older women.

**Conclusion:** These findings suggest incorporating a single MBD enhances breast cancer risk prediction, while including MBD changes benefits prediction in younger, pre-menopausal women. **Key finding:** Incorporating MBD from a single mammogram and largest MBD change improved breast cancer prediction accuracy compared to just the BCRAT model. **Impact on screening strategies:** As mammographic assessment advances, it may become more feasible to integrate dynamic mammographic measures into risk assessments to refine breast cancer screening and risk reduction strategies.

## Assessing Changes in Asymmetry of Breast Density over time and Associations with Breast Cancer Risk

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**Introduction:** High mammographic breast density (MBD), a known risk factor for breast cancer, may change over time, with stable/increasing MBD trajectories showing greater breast cancer risk than MBD that decreases with age. While some research has found asymmetry in MBD between the left and right breasts from a single screening mammogram has been associated with risk of interval breast cancer, others report no statistically significant associations though research is limited. It remains unclear whether MBD asymmetry changes over time and whether such changes are linked to breast cancer risk.

**Objectives:** To determine whether asymmetry in breast density measurements between left and right breasts changes over time, and whether those changes are predictive of breast cancer risk.

**Methods:** In a nested case-control study (259 cases, 992 controls) using the Sister Study cohort, we assessed asymmetry as the absolute differences ([Right – Left]) in Cumulus-measured MBD measures (percent density, cm<sup>2</sup> dense area, cm<sup>2</sup> non-dense area) at each mammogram exam (6,792 total) for women with  $\geq 2$  digital mammograms at least 6 months before diagnosis (for cases). We used linear mixed models to compare the trajectory of asymmetry over time between cases and controls, adjusting for baseline BMI and averaged density measure at each mammogram exam.

**Results:** Across all mammograms, MBD asymmetry was significantly higher for cases than controls for dense area (median: 5.00 cm<sup>2</sup> for cases, 4.62 cm<sup>2</sup> for controls). Compared to controls, cases exhibited statistically significantly greater increases in asymmetry over time dense area and non-dense area. Differences in asymmetry trajectories were fully attenuated for non-dense area when adjusting for body mass index (BMI) and averaged MBD measures at mammogram exam, but remained for dense area asymmetry (only

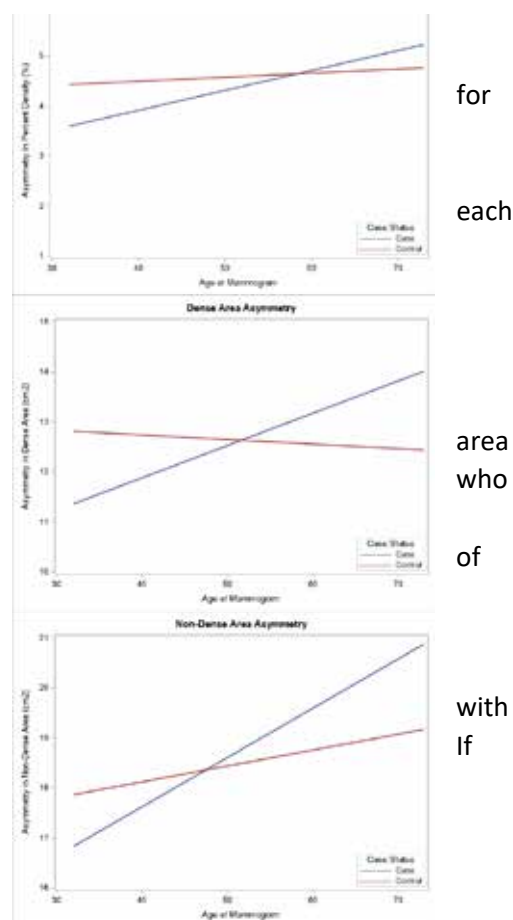
marginally non-significant). Temporal patterns were similar but of stronger significance when including mammograms within 6 months before diagnosis.

**Conclusions:** Pooling all mammograms at any age, left-right dense asymmetry is greater for cases than controls on average. Women develop breast cancer exhibit increasing asymmetry over time compared to controls. These findings highlight the potential utility

tracking changes in MBD asymmetry for breast cancer risk assessment but require replication in future studies. **Key finding:** Increasing asymmetry in dense area over time may be associated future breast cancer development. **Impact on screening strategies:** confirmed, monitoring changes in MBD asymmetry over time could inform strategies to improve early detection and prevention efforts.

(1) Hudson SM et al. Left-right breast asymmetry and risk of screen-detected and interval cancers in a large population-based screening population. Br J Radiol. 2020 Aug;93(1112):20200154.

Figure 1. Adjusted trajectory of asymmetry with age.



## Racial Differences in Background Parenchymal Enhancement, a Novel Marker for Breast Cancer Risk Category: Next-Generation Imaging and Biomarkers

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**Introduction:** Breast density is a known risk factor for breast cancer, but Black women are reported to have lower density based on BI-RADS, despite having higher absolute quantitative breast density. Background parenchymal enhancement (BPE) is a novel biomarker assessed via contrast-enhanced MRI. Women with high BPE levels face up to a four-fold increased risk of breast cancer, even after adjusting for breast density. However, no studies have focused specifically on BPE among Black women.

**Objective:** To examine racial differences in BPE levels. **Methods:**

We conducted a cross-sectional study including Black and White women aged 40-74 who had a BI-RADS score of 1 or 2 and no prior history of breast cancer. These women underwent mammography and subsequent MRI screening or diagnostic work-up between 2016 and 2022 at our institution. BPE was qualitatively classified into four categories based on BI-RADS: minimal, mild, moderate, and marked. Logistic regression was performed with race as the exposure variable and moderate or marked BPE as the outcome, adjusting for age, menopausal status, BMI, and BI-RADS density. **Results:** A total of 321 Black women and 1791 White women were included. Fewer Black women had extremely dense breasts compared to White women (2% vs. 21%,  $p = 0.01$ ), yet the proportion of Black women with high BPE (moderate or marked) was similar to that of White women (35% vs. 32%,  $p = 0.20$ ). A strong positive correlation between breast density and BPE was observed in both racial groups ( $p < 0.01$ ). After adjustment, Black women were 30% more likely to have high BPE compared to White women (95% CI: 1.30 [0.98, 1.72]). Black women with high BPE had 1.4 times greater odds of increased breast cancer risk compared to those with low BPE (95% CI: 1.40 [0.30, 6.70]), while White women with high BPE had a 1.07 times greater risk (95% CI: 1.07 [0.5, 2.2]). No significant race-BPE interaction was found for breast cancer risk. **Conclusion:** Despite the widely observed inverse relationship between race and BIRADS density, as well as the positive association between BPE and density in our study population, Black women are more likely to have high BPE compared to White women. **Key Finding:** This study provides novel evidence that Black women are more likely to have high BPE than White women, despite lower BI-RADS breast density. **Impact on Screening Strategies:** These findings suggest that incorporating biomarkers like BPE could help improve breast cancer screening strategies, potentially offering more equitable supplemental screening approaches.

Table 1. Demographic Characteristics by Race

| Characteristics                           | Black Women (N=321) | White Women (N=1791) | P value |
|-------------------------------------------|---------------------|----------------------|---------|
| Age at mammogram (mean, SD)               | 47.4 (10.0)         | 48.2 (11.3)          | 0.10    |
| Body Mass Index (mean, SD)                | 29.41 (6.8)         | 26.4 (73.4)          | 0.10    |
| Menopausal Status (N, %)                  |                     |                      | 0.02    |
| Premenopausal                             | 237 (74%)           | 1199 (67%)           |         |
| Postmenopausal                            | 84 (26%)            | 592 (33%)            |         |
| Breast Density (N, %)                     |                     |                      | <0.01   |
| Entirely fatty                            | 98 (31%)            | 394 (22%)            |         |
| Scattered fibroglandular tissue           | 14 (4%)             | 27 (2%)              |         |
| Heterogeneously dense                     | 173 (54%)           | 992 (55%)            |         |
| Extremely dense                           | 6 (2%)              | 378 (21%)            |         |
| Background Parenchymal Enhancement (N, %) |                     |                      | 0.20    |
| Minimal                                   | 54 (17%)            | 382 (21%)            |         |
| Mild                                      | 152 (47%)           | 850 (47%)            |         |
| Moderate                                  | 88 (27%)            | 421 (24%)            |         |
| Marked                                    | 27 (8%)             | 138 (8%)             |         |
| Cancer Status                             |                     |                      | 0.18    |
| No                                        | 309 (96%)           | 1747 (98%)           |         |
| Yes                                       | 12 (4%)             | 44 (2%)              |         |
| MRI Status                                |                     |                      | 0.39    |
| Screening                                 | 67 (21%)            | 246 (14%)            |         |

## Investigating the relationship between breast cancer risk factors and an AI-generated mammographic texture feature

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**Introduction:** The mammogram risk score (MRS), an AI-driven texture feature derived from digital mammograms, strongly predicts breast cancer risk independently of breast density, though underlying mechanisms remain unclear. **Objective:** This study investigated relationships between established breast cancer risk factors, covering anthropometrics, reproductive factors, family history, and mammographic density metrics, and MRS. **Methods:** Using data from the Nurses' Health Study II (292 cases, 561 controls), we validated MRS's association with breast cancer using logistic regression and evaluated its relationships with risk factors through: linear regressions of MRS on observed risk factors and polygenic scores associated with risk factors, and Mendelian randomization (MR) analysis via two-stage least squares regression. We conducted two-sample MR of MRS using summary statistics from genome-wide association studies of risk factors. **Results:** MRS was significantly associated with breast cancer risk before adjustment for BI-RADS density (OR=1.92 per SD increase in MRS; 95%CI:1.57-2.33; AUC=0.69) and after (OR=1.85; 95%CI:1.49-2.30). Early life body size and adult body mass index (BMI) were inversely associated with MRS, while history of benign breast disease and BI-RADS density showed positive associations; after adjusting for BI-RADS density, associations between MRS and the other three risk factors attenuated. Higher polygenic score for dense area was associated with increased MRS ( $\beta$ =0.16 SD increase in MRS per SD increase in polygenic score; 95%CI: 0.06-0.25), as was percent density ( $\beta$ =0.14; 95%CI:0.05-0.23). Two-sample MR identified associations between genetically predicted dense area ( $\beta$ =0.83 SD increase in MRS per SD increase in dense area; 95%CI:0.39-1.27) and percent density ( $\beta$ =1.14; 95%CI:0.55-1.74) with MRS. After adjusting for BI-RADS density and BMI, higher waist-to-hip ratio was significantly associated with increased MRS in polygenic score and two-sample MR analyses. No significant associations were observed with other risk factors. **Conclusion:** We validated MRS's association with breast cancer risk in cases diagnosed 0.5-10.1 years after mammogram acquisition. Our findings reveal robust associations between breast density measures and MRS and suggest a potential impact of central obesity on MRS. Risk factor associations will be validated through expansion of analyses to the Komen Tissue Bank. **Key findings:** There are robust associations between breast density measures, genetic predictors of density, and MRS, and suggestive associations between genetic predictors of central obesity and MRS. **Impact on screening strategies:** The strong predictive value of MRS, independent of its relationship to established risk factors, suggests its potential as a valuable tool for improving breast cancer risk assessment and personalized screening approaches.

## Assessment of Racial Differences in Lesion Detectability: A “Hybrid” Simulation for Breast Tomosynthesis

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**Introduction:** While additional screening for women with dense breasts has been advocated, more personalized screening strategies are needed, particularly for Black women who face disproportionately higher cancer mortality. Despite advancements in artificial intelligence for breast imaging, recent work continues to show higher false positives in Black women.<sup>1</sup> **Objective:** Quantify parenchymal complexity and lesion detectability across racial groups. **Methods:** We conducted a hybrid simulation to assess lesion detectability by inserting synthetic lesions into clinical tomosynthesis projections in a pre-existing case-cohort sample (n=8842; 2011–2022). White women (n=3355) had 421 and Black women (n=5487) had 458 diagnosed cancers after prior screening. A calibration cohort of 100 White and 100 Black women (with four standard views each) was randomly selected from the controls. A hybrid *in-silico* pipeline was used to evaluate lesion detectability; *Tomoseg* was used to segment breast and density masks.<sup>2</sup> Spiculated lesions were created using Perlin noise;<sup>3</sup> simple back-projection was used to determine the lesion locations in the reconstructions. Lesions were filtered by the system modulation transfer function and inserted into raw tomosynthesis projections with variable contrast.<sup>4</sup> Reconstructions were created with minimal processing (log conversion); image display was simulated to account for the display type and observer visual processing.<sup>5</sup> Regions of interest with and without lesions were measured with channelized Hotelling observers and receiver operating characteristic statistics were computed. **Results:** BI-RADS densities (1–4) for the case-cohort sample were (%White) 6, 50, 39, 5 and (%Black) 15, 61, 22, 1. The calibration cohort showed higher lesion detectability in Black women (ns;  $\Delta$ AUC 0.01–0.03). These results were consistent across three detectability thresholds. A study with a larger cohort and calibrated thresholds stratified by parenchymal complexity is ongoing. **Conclusion:** Lesion detectability in breast screening can vary by race; *in-silico* methods can aid in the study of how parenchymal complexity affects detectability since the synthetic lesions were identical in both groups. White women, who more commonly have denser breasts, had lower detectability compared to Black women. **Key finding:** By inserting synthetic lesions into clinical images, our results indicate that breast complexity is a prime factor driving detectability. **Impact on screening:** (1) Contrary to clinical experience, this simulation suggests lesions should be easier to detect in Black women due to lower density; however tumor biology/aggressiveness and growth rate are likely to impede diagnosis, suggesting the need for personalized screening. (2) This method could act as a personalized metric for assessing risk of masking, enabling assessment of detectability by type, size, and shape.

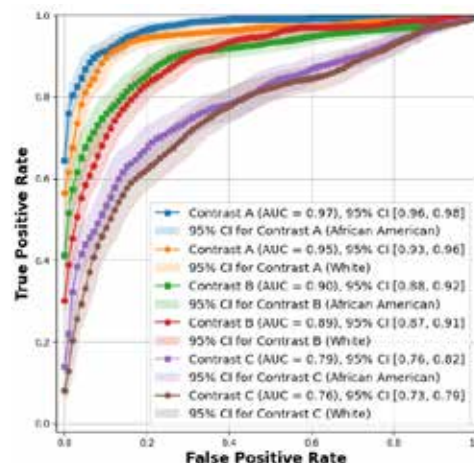


Figure 3. ROC curves for lesion detectability of White and African American women (calibration cohort). Curves calculated using identical spiculated lesions (15x15x5 mm<sup>3</sup>) and contrasts A-C.

**Acknowledgments:** Real-time tomography, LLC for providing technical support and reconstruction resources. Funding for this research is provided by the 2023 Terri Brodeur Breast Cancer Foundation and the 2023 Komen Career Catalyst Research grant (CCR231010477).

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## Investigating the molecular mechanisms driving delayed TDLU involution in African American women

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**Background:** Terminal duct lobular units (TDLU) are epithelial sub-structures located within breast tissue and function in lactation. TDLU involution is a mechanism that reduces TDLU counts post-pregnancy and post-menopause<sup>1</sup>. This process ensures decreased potential for transformation of breast epithelial cells into cancerous lesions, and delayed TDLU involution has been associated with increased breast cancer risk<sup>2</sup>. Delayed TDLU involution is more frequently observed in African American (AA) women<sup>2,3</sup>, but the molecular pathways influencing this process have not yet been fully elucidated. **Objectives:** This project aims to identify the major molecular mechanisms and pathways that influence TDLU involution, including links to epigenetic modifications, genetic predispositions, and breast cancer. **Methods:** Using TDLU measurements derived from healthy breast tissue of pre-menopausal AA and European American (EA) women donating to the Komen Tissue Bank, we performed RNAseq (n=94) and the EPIC850K Methylation Array (n=290) to determine differences in gene expression and DNA methylation related to high and low TDLU counts (counts/mm<sup>2</sup>) by race. We also employed pathway analyses to determine relationships between differentially expressed genes (DEGs) by TDLU counts in AA and EA women. Gene expression and methylation analyses were performed using the R packages, *DESeq2* and *limma*, respectively. **Results:** After adjusting for age, AA women showed the greatest number of significant differentially methylated CpG sites compared to EA women (12,554 vs 72) by dichotomized TDLU counts. Of interest, milk-fat globular epithelial growth factor 8 (MFGE8), a gene that functions in epithelial cell apoptosis, lactation, and involution regulation, was significantly differentially expressed and differentially methylated in AA women only. We observed lower MFGE8 gene expression for AA women with low TDLU counts and higher methylation beta values. Given the premenopausal nature of this cohort, lower MFGE8 expression could indicate prevention of premature involution or silencing post-involution (post-pregnancy). Further mechanistic studies, potentially in a post-menopausal cohort, could confirm the role and differential regulation of MFGE8 by ancestry. **Conclusion:** Understanding the molecular consequences of delayed TDLU involution in breast cancer risk by ancestry group will be important in ameliorating breast cancer disparities. **Key Finding:** Differential expression of MFGE8 may play a key role in the delayed TDLU involution experienced by AA women. **Impact on screening strategies:** Although measuring TDLU involution is not yet standard clinical practice to assess breast cancer risk, identification of a related biomarker could be used to screen for those at increased risk for delayed TDLU involution and potential breast carcinogenesis.

**Acknowledgements:** We would like to thank the Komen Tissue Bank and the women who voluntarily donated these samples.

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## Dedicated Breast CT Derived Breast Density Metrics and its Relationship with Breast Cancer Risk in Overweight or Obese Hispanic Women

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**Introduction:** Radiographic breast density and obesity are established markers for breast cancer risk. However, the relationship between breast density and obesity is complex. This complexity may partly stem from the increased compressed breast thickness for obese women during mammographic assessment of breast density. Evaluating breast density on non-compressed breasts using fully 3-D dedicated breast CT may shed light on the relationship between breast density and obesity. **Objectives:** This single-institution, prospective, cross-sectional study aimed to evaluate the feasibility of using breast CT to obtain quantitative density measures, and to determine its relationship with breast cancer risk in overweight/obese women. **Methods:** This IRB-approved, HIPAA-compliant study (NCT04799665) targeted the recruitment of 80 Hispanic women due to the higher prevalence (>35%) of obesity and based on statistical considerations. Body habitus, vitals and standard metabolic panel were obtained. Familial and personal risk factors were used to estimate the lifetime and 10-year breast cancer risks [1]. Bilateral cone-beam breast CT was performed on a low-dose ( $4.1 \pm 0.9$  mGy), offset-detector prototype system to obtain high-resolution (0.22mm isotropic voxels) fully-3D images, which were segmented to obtain fibroglandular volume (FV), adipose volume (AV), and volumetric glandular fraction (VGF), defined as the proportion of fibroglandular to total breast volume excluding the skin [2]. **Results:** Study exceeded the recruitment target (n=92). Summary statistics for age, BMI, 10-year, and lifetime risks were  $50 \pm 6.9$  years,  $32.5 \pm 5.1$  kg/m<sup>2</sup>,  $2.95 \pm 1.5\%$ , and  $12.2 \pm 5.6\%$ . Three or more components of metabolic syndrome were present in 52/92 (56.5%) subjects. Breast density-associated measures were obtained for all 92 subjects (100% success rate). Age-adjusted regression analyses showed both AV and FV were positively ( $p < 0.05$ ) related to 10-year and lifetime risks. VGF was not associated with 10-year and lifetime risks. **Conclusion:** The study achieved the primary endpoint of evaluating the feasibility of using breast CT to obtain volumetric breast density measures. Given the significant associations of FV and AV with 10-year and lifetime risks, these metrics may serve as preferred markers over VGF for evaluating risk-reduction strategies in overweight/obese women. **Key finding:** Since FV includes ductal epithelium and lobules where most breast cancers originate and AV reflects tissue prone to chronic low-grade inflammation in overweight/obese women, quantifying these density metrics may be beneficial for evaluating risk-reduction strategies. **Impact on screening strategies:** If ongoing efforts to translate breast CT for screening are successful, this can provide an easy and accurate tool for determining breast density-associated measures that are needed for risk-estimation.

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Characterizing the transcriptomic and immune landscape of benign breast lesions in relation to mammographic density

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**Introduction:** While benign breast disease (BBD) and mammographic breast density (MBD) are both strong, independent risk factors for breast cancer, evidence suggests they may also interact to jointly influence breast cancer risk.

**Objectives:** We aimed to characterize the transcriptome and immune microenvironment of benign breast biopsies to better understand relationships underlying BBD and MBD biology.

**Methods:** The Breast Radiology Evaluation and Study of Tissues-Stamp Project included women aged 40-65 years who underwent diagnostic, image-guided breast biopsy at UVM Medical Center following an abnormal breast imaging exam. Among patients diagnosed with BBD (n=418), RNA was extracted from FFPE breast biopsy tissues for gene expression profiling (Nanostring Breast Cancer 360 panel, 758 genes). MBD was quantified in the biopsied breast as % fibroglandular tissue volume (%FGV) and analyzed in tertiles ("Low", <28.6; "Medium", 28.7-48.0; "High", >48.0 %FGV), with high MBD defined as the highest tertile. Differential gene expression and pathway enrichment analyses were performed by MBD tertile, adjusting for age, BMI, ages at menarche and first birth, biopsy year, menopausal status, and BBD histologic subtype. A subset of BBD tissues (n=64) underwent multiplex immunofluorescent staining for immune cell subpopulations and associations with MBD were evaluated by multivariable linear regression.

**Results:** 156 individual genes were differentially expressed in BBD lesions with high MBD (false discovery rate (FDR)<0.1). Leptin, an adipokine, was identified as the top gene downregulated with high MBD (|fold change (FC)|=3.25 FDR=3.1E-06) and HLA-DQA1, an MHC class II gene critical in immune response, was identified as the top gene upregulated with high MBD (|FC|=1.82, FDR=0.07). Pathway analyses of FDR-significant genes revealed increasing MBD was associated with cancer hallmark pathways related to tissue transformation, pro-inflammatory cytokine signaling, and estrogen signaling. Immune cell profiling of the BBD microenvironment revealed suggestive associations (P<0.1) between higher MBD and increased abundance of exhausted T cells ( $\beta$ =0.05,  $P$ =0.07) and macrophages ( $\beta$ =1.83,  $P$ =0.06).

**Conclusions:** We identified molecular and microenvironmental features associated with elevated breast density in BBD patients. Future directions will relate these findings to 10-year breast cancer risk.

**Key finding:** In this study, we uncovered density-associated genes (N=156, e.g.,  $\uparrow$  HLA-DQA1/B1, AREG;  $\downarrow$  LEP, FHL1), signaling pathways (N=19, e.g., KRAS signaling, epithelial-to-mesenchymal transition, IL-6/JAK/STAT3 signaling), and immune cell subpopulations (N=2, i.e., exhausted T cells, macrophages) in benign breast lesions.

**Impact on screening strategies:** A better understanding of the biological underpinnings of breast density and its influence on future breast cancer risk could improve current risk stratification strategies.

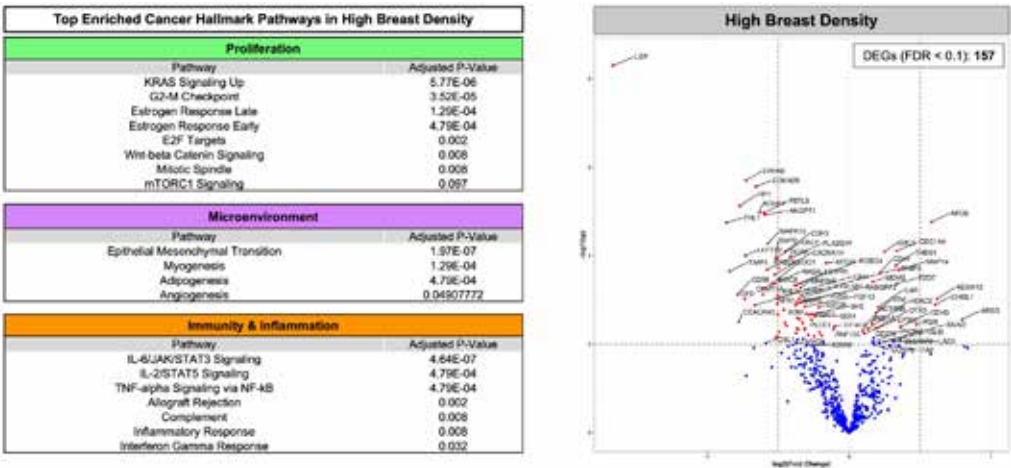


Figure 1. Differentially expressed genes (right) and enriched cellular signaling pathways (left) associated with breast density in 418 benign breast lesions from the Breast-STAMP

## Investigating the added value of incorporating mammographic density to an integrated breast cancer risk model with questionnaire-based risk factors and polygenic risk score

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**Introduction.** Incorporation of mammographic density to breast cancer risk models could improve risk stratification to tailor screening and prevention strategies according to risk. Robust evaluation of the value of adding mammographic density to models with comprehensive information on questionnaire-based risk factors and polygenic risk score is needed to determine its effectiveness in improving risk stratification of such models.

**Methods.** We used the Individualized Coherent Absolute Risk Estimator (iCARE) tool for risk model building and validation to incorporate density to a previously validated literature-based model with questionnaire-based risk factors and a 313-variant polygenic risk score (PRS). The model was evaluated for calibration and discrimination in three prospective cohorts of European-ancestry women (1,468 cases, 19,104 controls): US-based Nurses' Health Study (NHS I and II) and Mayo Mammography Health Study (MMHS); and Sweden-based Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) study. Analyses were done separately for women younger (NHS II, KARMA) and older than 50 years (NHS I, MMHS, KARMA). Improvements in terms of risk stratification and reclassification proportions were assessed among European-ancestry women aged 50-70 years in US and Sweden. **Results.** For women younger and older than 50 years, the model with questionnaire-based risk factors, PRS and density was generally well calibrated across risk with some evidence of miscalibration at the extremes of the risk distribution. Incorporation of density led to modest improvements in risk discrimination beyond the model with questionnaire-based risk factors and PRS: the area under the curve (AUC) among younger women was 67.0% (95% CI: 63.5-70.6%) vs. 65.6% (95% CI: 61.9-69.3%) for models with and without density; and 66.1% (95% CI 64.4-67.8%) vs. 65.5% (95% CI: 63.8-67.2%) among older women. The model with density identified 18.4% of US women 50-70 years old  $\geq 3\%$  5-year predicted risk (threshold used for recommending risk-reducing medication in the US), with 42.4% of future cases expected to occur in this group. At this threshold, 7.9% of US women were reclassified by adding density to the model, resulting in the identification of 2.8% of additional future cases. The model with density identified 10.3% of Swedish women  $\geq 3\%$  5-year predicted risk, with 29.4% of future cases expected to occur in this group. At this threshold, 5.3% of women were reclassified with the addition of density, leading to the identification of an additional 4.4% of future cases. **Conclusion.** Integrating density with questionnaire-based risk factors and PRS could potentially identify more women of European-ancestry with elevated risk of breast cancer in the United States and Sweden. Further investigations of the integrated model in non-European ancestry populations are needed prior to considering clinical applications.

## Does Consideration of Short-term Risk Improve Risk Prediction for the Longer Term?

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**Introduction:** More effective use of available data when developing breast cancer risk models could improve prediction performance while reducing data requirements. **Objectives:** Focusing on maximizing the utility of a single dataset, we aim to investigate whether incorporating information about short-term (within 2 years) breast cancer development risk can improve the prediction of longer-term (within 4 years) risk using a deep-learning-based model for digital mammography. **Methods:** The proposed framework involves two identical models trained for different time-to-event ranges: short-term and long-term risk. Both models are trained on the same set of images with adjusted labels, such that the long-term model includes a higher proportion of positive cancer samples. Each model consists of four identical pretrained resnet-18 encoders<sup>1</sup> to extract mammographic features, which are then concatenated, reduced through attention pooling, and passed through a fully connected layer for the final prediction. The baseline probabilities rely solely on the long-term model's output, but in the proposed approach, the long-term model's probabilities for the final risk prediction are adjusted to be, at the minimum, that of the short-term model's probability. This because the likelihood of an event occurring within the next 4 years must be equal to or higher than the likelihood of it occurring within the next 2 years. The dataset consists of digital screening mammograms retrospectively retrieved from the Dutch Screening Program. In total, 7107 cases were included (1:2 ratio of malignant to normal for short-term model and 1:1 for long-term model). **Results:** No significant difference was detected between the predictions of breast cancer risk based solely on the long-term model and those adjusted with the short-term model (AUC: 0.742 vs 0.744; P=0.67). This might be due to the probabilities not being normalized between the two networks, potentially affecting the comparability and adjustment process. **Conclusion:** Incorporating additional two-year risk information into the four-year model did not improve the predictions of breast cancer risk. **Key finding:** There was no significant improvement in breast cancer risk prediction when incorporating the short-time risk into the long-time risk, indicating that the longer-time risk alone may already capture the relevant risk information. **Impact on screening strategies:** Although the proposed approach did not show significant improvement in breast cancer risk prediction, it emphasizes the need for continued research into risk estimation methods, as more accurate models could enable personalized screening, ultimately improving overall outcomes.

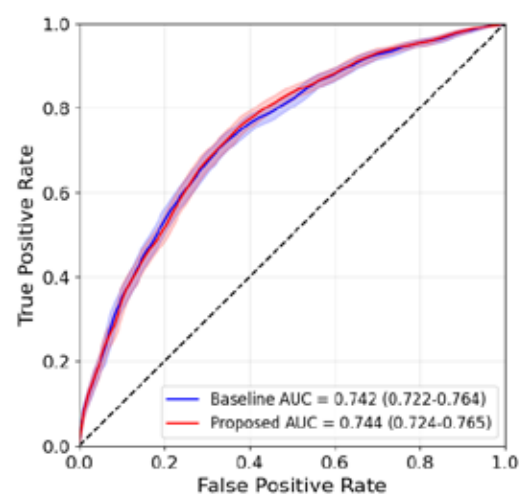


Figure 1: Performance of baseline and proposed 4-year breast cancer risk models.

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## Advancing Evidence of the Associations between specific Benign Breast Diagnoses and Future Breast Cancer Risk

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**Background:** While some risk prediction models include high-risk benign breast diseases (BBD), associations between common BBD and breast cancer risk remain insufficiently studied. **Methods:** Benign breast biopsies (N=125,361) performed between 1994-2022 in women without prior breast cancer were identified from pathology databases within 7 Breast Cancer Surveillance Consortium registries. Pathological diagnoses were classified by two breast pathologists into 40 BBDs grouped into 4 histologic categories (lobular carcinoma *in situ* [LCIS], proliferative changes with atypia, proliferative changes without atypia, non-proliferative lesions). For comparison, women with no prior breast biopsy and a negative screening mammogram (N=1,847,114) were identified. Hazard ratios (HR) for associations between BBDs and invasive breast carcinoma vs. ductal carcinoma *in situ* (DCIS) were estimated using Cox proportional hazards regression. **Results:** The most common BBD diagnoses were fibrocystic changes (28.4%), fibroadenoma (24.2%), and usual ductal hyperplasia (15.3%). Apocrine metaplasia, columnar cell lesions, sclerosing adenosis, and papillomatosis occurred >80% of the time with other BBDs. LCIS and proliferative BBD diagnoses were more strongly associated with DCIS, while non-proliferative BBDs showed less strong and similar associations with DCIS and invasive carcinoma. LCIS was associated with a 5.60-fold increased risk (95%CI=3.96, 7.92) of invasive carcinoma and 10.9-fold increased risk (95%CI=6.65, 17.9) of DCIS. Among women with proliferative changes with atypia, invasive HRs for specific BBD diagnoses ranged from 3.28 (atypia NOS) to 3.99 (atypical hyperplasia NOS), and DCIS HRs ranged from 3.38 (atypical lobular hyperplasia) to 7.06 (atypical ductal hyperplasia). Among proliferative changes without atypia BBDs, invasive HRs ranged from 1.08 (papillomatosis) to 2.85 (multiple papillomas), and DCIS HRs ranged from 1.06 (papillomatosis) to 5.13 (multiple papillomas). Among non-proliferative BBDs, invasive HRs ranged from 0.86 (apocrine metaplasia) to 2.33 (adenoma), and DCIS HRs ranged from 0.71 (fat necrosis) to 3.97 (phyllodes tumor). **Conclusion:** The magnitude of associations between BBD diagnoses and breast cancer risk varied widely within commonly used categories. Risk prediction models may be improved by expanding BBD categories to include more detailed diagnoses. **Key finding:** Our research offers updated insights into relationships between BBDs and breast cancer risk with greater precision. This study is the first to separately examine the associations of specific BBDs with invasive and non-invasive breast cancer, deepening understanding of these relationships. **Impact on screening strategies:** Advancing knowledge of specific BBD associations with future breast cancer risk may improve risk prediction for targeted screening and primary prevention. This knowledge has the potential to refine public health interventions aimed at reducing breast cancer mortality and advancing personalized care strategies.

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# Mammography AI Models and Radiomic Features for 5-year Breast Cancer Risk Prediction: A Matched Case-Control Study in an Ethnically-Diverse Cohort

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**Introduction:** The age-adjusted incidence of invasive breast cancer is higher in Hawai'i (139.6 per 100,000) than in the United States overall (126.9 per 100,000) as of 2018. Additionally, the burden of advanced-stage breast cancer varies considerably among Hawai'i's Asian, Native Hawaiian, and Pacific Islander (AANHPI) ethnic minorities. Among AANHPI women, the proportion of cases diagnosed at an advanced stage is lowest in Japanese (17.2%) and highest in Native Hawaiian (24.6%) women. AI- and radiomic-empowered risk models have shown good performance in estimating all-stage breast cancer risk in mostly racially/ethnically homogeneous populations, but it is unclear how they perform in an ethnically-diverse AANHPI population. **Objectives:** The purpose of this study is to investigate the differential performance of various AI models and radiomic features for the prediction of all-stage breast cancer risk in a multi-ethnic, AANHPI cohort. **Methods:** From over 125,000 women participating in the Hawai'i and Pacific Islands Mammography Registry (HIPIMR; NIH R01CA263491 and U54CA143728), we selected women ages 40-79 years with a negative screening or diagnostic mammogram. Cases were defined as women who developed breast cancer more than 6 months after their imaging date. Controls were matched to cases 3:1 on birth year, race/ethnicity, and mammography machine manufacturer. We evaluated 5 academic AI models (1-5), 3 commercial AI scores (ProFound AI, iCAD Inc., USA; ProFound Risk, iCAD Inc., USA; and Transpara, ScreenPoint Medical, NL) and 3 radiomic feature sets (6-8) for association with invasive breast cancer alone and in combination with other known clinical risk factors. **Preliminary Results:** 74,820 women in the HIPIMR were found to have a negative mammogram with the four standard views with known breast density, and race/ethnicity. After exclusion of patients with anomalous images, our final dataset consists of 3,776 controls and 1,307 invasive cases. See *Table 1*. We will present performance statistics on each AI/radiomic feature, alone and in combination with traditional risk factors, stratified by race and ethnicity. **Conclusion:** Our study will show whether established breast cancer risk AI models are predictive of all-stage breast cancer risk in minority AANHPI populations. **Key finding:** Reporting of a survey on the performance of the state-of-the-art in AI- and radiomic-empowered all-stage breast cancer risk assessment in AANHPI ethnic groups. **Impact on screening strategies:** The performance of AI- or radiomic-enhanced breast cancer risk assessment from screening mammograms needs to be evaluated in an ethnically-diverse AANHPI cohort, representative of screened women in Hawai'i. This could have implications for the clinical use of these tools in areas with high ethnic diversity or large AANHPI populations.

Table 4. Characteristics of the cohort selected from the HIPIMR.

|                | Women, N            | Cases | Controls |
|----------------|---------------------|-------|----------|
|                |                     | 1,386 | 3,940    |
| Age at exam    | 40-49               | 361   | 811      |
|                | 50-59               | 448   | 1,273    |
|                | 60-69               | 420   | 1,366    |
|                | 70-79               | 157   | 490      |
| Race/ethnicity | NHPI                | 277   | 804      |
|                | White               | 186   | 526      |
|                | Chinese             | 114   | 247      |
|                | Filipino            | 175   | 251      |
|                | Japanese            | 494   | 850      |
|                | Other/NOS Asian     | 79    | 1,215    |
| Breast density | Other               | 16    | 47       |
|                | Fatty (A)           | 39    | 229      |
|                | Scattered (B)       | 661   | 1,643    |
|                | Heterogeneous (C)   | 553   | 1,729    |
|                | Extremely dense (D) | 134   | 339      |

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## Current State of Mammography-based AI for Future Breast Cancer Risk Prediction: A Systematic Review

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**Introduction:** Interest in personalized, risk-stratified breast cancer (BC) screening is growing worldwide, in part driven by the emergence of mammography-based AI models that rival the performance of clinical risk factor models in predicting future BC risk (1). However, the current evidence for their clinical effectiveness is unclear (2). **Objectives:** To review the current evidence on mammography-based AI models for future BC risk prediction and identify knowledge gaps to inform future research directions. **Methods:** Systematic literature review of six databases from Jan 1, 2012, to Apr 2, 2024. Eligible studies reported on mammography-based AI models used to estimate future BC risk prediction in a real-world screening setting. We evaluated study design, race/ethnicity, geographic origin, mammogram type (digital mammogram [DM] versus digital breast tomosynthesis [DBT]), prediction time frame, and BC type predicted. **Results:** Of 14,119 citations identified, 31 studies met our inclusion criteria. All studies were analyzed retrospectively, with a mix of study designs (14 case-control, 4 case-cohort, 13 cohort). Most images were DM (n=30 studies), acquired using Hologic equipment (n=17) and performed in the United States (n=18). White, non-Hispanic women were most commonly represented (>50% of study population) in 10 of 16 studies reporting race/ethnicity. Most common prediction time frame was 4-6 years (n=15 studies) and most models predicted any BC type (n=25); four studies evaluated invasive BC only. All studies assessed discrimination performance, with the AUC value at the longest prediction time point ranging from 0.61 to 0.82, while only three studies assessed model calibration performance. **Conclusion:** Mammography-based AI models may provide accurate BC risk prediction. Future studies should evaluate models that use DBT, examine performance for invasive or advanced BC risk prediction, include diverse populations, and evaluate model calibration as well as discrimination performance. Prospective evaluations are needed to determine the clinical utility of mammography-based AI models for personalized risk-based BC screening before implementation. **Key finding:** Current evidence is limited to evaluating AI accuracy on only 2D DMs acquired by a single manufacturer, limited geographic inclusion, prediction of any BC type collectively instead of subtypes, varied prediction time frames, and few assessments of model calibration. **Impact on screening strategies:** Future mammography-based AI risk prediction model evaluations should examine 3D mammography, predict specific BC types associated with worse outcomes, and assess model calibration performance across multiple racial/ethnic groups, geographies, and manufacturers.

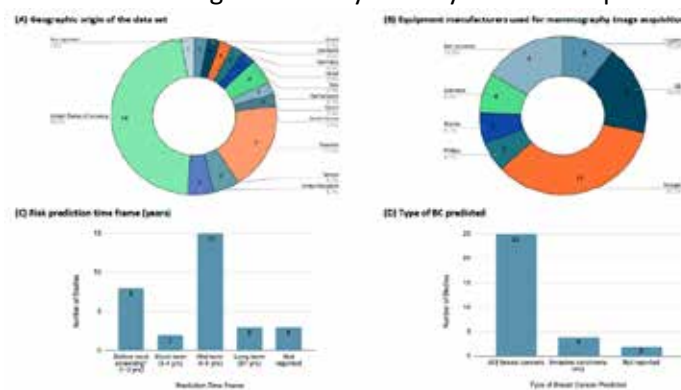


Figure. Distribution of the geographic origin of the data (A), equipment vendor used for image acquisition (B), risk prediction time frame (C), and type of BC predicted (D).

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# Optimal Modeling of an Early Detection Protocol Using a Portable Ultrasound Systems in Rural Environments: The Impact of Ambient Temperature and Charge-Discharge Cycles

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**Introduction:** In the U.S. Affiliated Pacific Islands, limited mammography access results in 15% advanced-stage breast cancer diagnoses, compared to 9% in the continental U.S. AI-enhanced handheld ultrasound devices offer cost-effective, portable solution for early detection, operable by minimally trained local-healthcare providers. The potential issues with portable ultrasound devices include overheating and limited battery life, requiring temperature control to maintain functionality in remote settings. **Objectives:** This study aimed to evaluate how ambient temperature and charging cycles affect the maximum number of women that can be scanned during continuous use. **Methods:** We assembled a portable point-of-care ultrasound (POCUS) system comprised a handheld scanner (Clarius L7 HD3; Clarius Mobile Health Inc., Canada), a tablet (Samsung Galaxy Tab S9 Ultra; Samsung Electronics Co., Ltd., South Korea), and a laptop (Dell XPS 15; Dell Inc., USA). The scanner used ad hoc Wi-Fi to communicate and stream real-time images to the tablet and laptop via Clarius Cast API. To replicate clinical conditions, a training breast phantom (Gphantom; EDM Medical Solutions, USA) was used. POCUS images were processed at 15 frames per second using SSDLite320+MobileNetV3 AI model fine-tuned on gelatin-based breast phantom data. Battery and temperature data were collected at 99% charge and 26°C ambient temperature. The threshold temperature was set at 40°C as it automatically shuts off due to overheating. Time constants for battery and temperature behavior were calculated and used to develop prediction models, evaluating ambient temperatures from 26°C to 32°C during 8-hour workday. **Results:** At 26°C, the scanner has a simulated discharge time of 10 minutes with a minimum charge time of 4 minutes, maintaining a battery level of 93% and temperature of 37°C (see Table 1). At higher temperatures of 30°C and 32°C, the required charge time increases to 5–6 minutes, with battery levels at 87–89% and scanner temperatures at 38–39°C. With a 10-minute discharge time, the scanner handles 34 women per day at 26°C, dropping to 30 at 32°C due to longer charging intervals. **Conclusion:** As ambient temperature rises, charge time increases relative to discharge time to prevent overheating, reducing the number of women scanned. **Key finding:** Charging at least half as long as discharging minimizes overheating and maximizes number of scans. **Impact on screening strategies:** In resource-limited regions, predictive models can optimize scheduling and patient throughput. Future testing on real patients could refine AI detection models, improving real-time outcomes based on factors like temperature and battery performance.

Table 1: Simulated discharge time, minimum charge time, battery performance, scanner temperature and number of women scanned per workday across different ambient temperatures

| Ambient Temperature (°C) | Discharge Time (min/patient) | Minimum Charge Time (min between patients) | Steady Stated Battery Percentage (%) after one cycle | Steady-State Scanner Temperature (°C) after one cycle | Number of Women per workday |
|--------------------------|------------------------------|--------------------------------------------|------------------------------------------------------|-------------------------------------------------------|-----------------------------|
| 26°C                     | 5, 10, 15                    | 2, 4, 5                                    | 97, 93, 90                                           | 28, 37, 38                                            | 68, 34, 24                  |
| 28°C                     | 5, 10, 15                    | 2, 4, 6                                    | 85, 87, 90                                           | 30, 39, 38                                            | 68, 34, 22                  |
| 30°C                     | 5, 10, 15                    | 3, 5, 7                                    | 91, 89, 90                                           | 32, 38, 38                                            | 60, 32, 21                  |
| 32°C                     | 5, 10, 15                    | 4, 6, 8                                    | 91, 87, 88                                           | 36, 39, 39                                            | 53, 30, 20                  |

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A Hybrid Self-Supervised and Supervised Deep Learning Framework for Accurate Volumetric Breast Density Segmentation From 3D Reconstructed DBT Images

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**Introduction:** Breast density (BD), defined as the proportion of glandular and fibrous tissue to fatty tissue in the breast, is a significant factor in breast cancer risk. Automated tools for volumetric BD estimation from digital breast tomosynthesis (DBT) images promise to overcome observer variability and improve risk prediction. **Objectives:** The objective of this study is to develop a fully automated deep learning tool for volumetric breast density (VBD) estimation using 3D reconstructed, “for presentation” digital breast tomosynthesis (DBT) images. **Methods:** This study utilized two datasets of anonymized digital breast tomosynthesis (DBT) images from the Hospital of the University of Pennsylvania. Dataset 1 included 7,853 scans (2011-2016), while Dataset 2 comprised 3,922 scans (2011-2022) from Black women aged 40–74 with no history of breast cancer. Images were resized to 1024x1024 pixels, anonymized, and augmented with horizontal flips and  $\pm 15^\circ$  rotations. The segmentation model, inspired by Mask-DINO[1], employed a Swin Transformer[2] backbone and UNet-style decoder for tissue classification into background, fatty, and dense categories. Training was conducted in two phases. In the self-supervised pretraining phase, 40% of the input views were masked based on tissue type to encourage feature learning, combined with contrastive learning to improve differentiation between structures. In the supervised fine-tuning phase, reference-standard segmentations optimized the model for 50 epochs using a combination of weighted cross-entropy and Dice loss. Performance was evaluated with Dice score metric. **Results:** Table 1 shows that our deep learning model demonstrated high accuracy in segmenting dense breast tissue from reconstructed DBT images, achieving robust performance across both datasets. For Dataset 1, the model achieved a weighted Dice score of  $0.87 \pm 0.10$ , with class-specific Dice scores of  $0.99 \pm 0.01$  for background,  $0.95 \pm 0.08$  for fatty tissue, and  $0.84 \pm 0.12$  for dense tissue. On Dataset 2, the weighted Dice score was  $0.86 \pm 0.06$ , with background, fatty tissue, and dense tissue Dice scores of  $0.99 \pm 0.08$ ,  $0.94 \pm 0.05$ , and  $0.83 \pm 0.08$ , respectively. These results highlight the model's ability to consistently differentiate tissue types, particularly in separating dense tissue, with minimal variability even in the most challenging classifications, demonstrating robustness and reliability for clinical applications. **Conclusion:** We developed a deep learning model for segmenting dense breast tissue from 3D DBT images, addressing challenges like distinguishing dense tissue from the pectoral muscle and achieving robust performance across racial groups. By enabling accurate volumetric breast density estimation associated with breast cancer risk, our approach holds promise for personalized risk assessment and large-scale epidemiologic studies. **Key finding:** A hybrid deep learning model, combining self-supervised pretraining with supervised fine-tuning, accurately segments dense breast tissue from 3D reconstructed DBT images. **Impact on screening strategies:** The model’s ability to accurately and objectively segment dense breast tissue enables improved risk stratification, reduces variability in breast density assessments, and ensures equitable performance across diverse populations. By operating without the need for large-scale radiological annotations, it offers scalable deployment and seamless integration into existing DBT workflows, supporting precision breast cancer screening and optimizing resource allocation.

| Metric                         | Dataset 1<br>(mean $\pm$ SD) | Dataset 2<br>(mean $\pm$ SD) |
|--------------------------------|------------------------------|------------------------------|
| Background Dice                | 0.99 $\pm$ 0.01              | 0.99 $\pm$ 0.08              |
| Fatty tissue Dice              | 0.95 $\pm$ 0.08              | 0.94 $\pm$ 0.05              |
| Dense tissue Dice              | 0.84 $\pm$ 0.12              | 0.83 $\pm$ 0.08              |
| Weighted Dice<br>(all classes) | 0.87 $\pm$ 0.10              | 0.86 $\pm$ 0.06              |

Table 1. Dice scores for both datasets

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## Robustness of a biophysics-based computational approach that is agnostic to PROCESSING vs PRESENTATION mammograms for breast cancer risk assessment

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**Introduction:** Advances in deep learning create high expectations from the breast cancer research field [1, 2]. However, the rapid growth of AI-based methods has outpaced our assessment of their strengths and limits, which creates major concerns about these methods' reproducibility [3]. In mammography, "*we may repeat the same mistakes we made with computer-aided detection/diagnosis*" [4]. Particularly worrisome is the high sensitivity to software that transform "FOR-PROCESSING" to "FOR-PRESENTATION" mammograms. One study using a commercial AI found a threefold increase in recall rates following mammography software upgrade [5]. We developed a biophysics-based (non-AI) computational method that can segregate mammographic dense tissue into two textural subtypes: *active*, which is structurally reorganizing, versus *passive* [6, 7]. Tissue restructuring associates with tumorigenesis, is detectable before radiological diagnosis, and the composition and temporal dynamics of dense tissue subtypes influences cancer risk [8, 9]. **Objective:** Our goal is to demonstrate the robustness of our biophysics-based computational risk prediction approach on matching PROCESSING-PRESENTATION mammograms in a case-control retrospective study. **Methods:** Using the OPTIMAM database [10, 11], matching PROCESSING-PRESENTATION standard bilateral mammographic screening views were acquired on Hologic's Selenia units on an age-matched population approximately 3 years prior to diagnosis for n=199 cases (mean age = 59.35), or their last assessment episode on record for n=3719 controls (mean age = 59.80). Mammograms were analyzed following our approach in refs [6, 7, 12, 13]. A generalized linear model (GLM) was developed to predict cancer vs. control status with the predictive variables being the amounts of fatty, passive dense, active dense tissue, as well as mammographic percent density [8], and the patient's age. A GLM was created for PROCESSING and PRESENTATION mammograms respectively with AUCs calculated. **Results:** The predictive model yielded virtually identical AUCs of 0.631 and 0.630 for the PROCESSING and PRESENTATION datasets, respectively. **Conclusion:** The virtually identical AUCs from the FOR-PROCESSING vs FOR-PRESENTATION mammograms offer strong evidence that our method may be agnostic to mammography software alterations. **Key finding:** Our non-deep learning approach based on automated stratification of mammographic density is resistant to changes mammograms undergo from PROCESSING to PRESENTATION. **Impact on screening strategies:** AI-derived image-based models that automate risk detection which have been tested on PROCESSING vs PRESENTATION mammograms would improve clinical translation by minimizing delays to update models when mammographic vendors update their software.

**Acknowledgements:** The images and data used in this publication are derived from the OPTIMAM imaging database (OPTIMAM (OMI-DB) project website: <https://medphys.royalsurrey.nhs.uk/omidb/about-omi-db/>) [10]. We acknowledge the OPTIMAM project team and staff at the Royal Surrey NHS Foundation Trust who developed the OPTIMAM database, and Cancer Research UK who funded the creation and maintenance of the database. We acknowledge National Institutes of Health awards R15CA246335 and R41CA285182. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

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## Adaptation-induced biases in BI-RADS ratings of breast density

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**Introduction:** Several clinical breast-cancer screening studies<sup>1-3</sup> have demonstrated that observer performance improves as readers progress through consecutive cases. Specifically, false-positive rates decrease, without a measurable decrease in sensitivity. There is currently no established explanation for this improvement. We are investigating visual adaptation as a potential mechanism. Adaptation is a well-established principle of sensory processing and is thought to optimize sensitivity and perception for the current stimulus environment. We have previously shown that the perceived density of images can be biased by adaptation to images with a different density, but in untrained (non-radiologist) observers<sup>4,5</sup>. **Objectives:** Examine whether adaption occurs in radiologists' viewings of stimuli extracted from digital breast tomosynthesis (DBT) images. **Methods:** We used a standard visual adaptation paradigm in which subjects passively viewed 60 serial images in 15 seconds to induce adaptation, and then judged the density of independent target images shown briefly between short periods of re-adaptation. The adapting stimuli were dense (Dense-Adapt) or fatty (Fatty-Adapt) DBT images, or a uniform grey field (No-Adapt Condition). Target images were patches of DBT images taken from parenchymal regions, and were blended between dense and fatty samples to generate a graded range. Thirteen radiologist or resident subjects were recruited and participated during the 2024 European Congress of Radiology. They categorized the blended targets using the 4 BI-RADS density categories. Data analysis accounted for the random effects of stimuli and radiologists. **Results:** Density responses increase with blending fraction ( $p < 0.01$ ), with similar rate for adaptation conditions and lower rate for no-adapt ( $p < 0.01$ ). There is also a consistent difference in density responses between the two adaptation conditions ( $p < 0.001$ ). Specifically, dense blends tended to be rated as more dense after adapting to the fatty images and vice versa. **Conclusion:** Adaption to density differences across DBT image patches can induce density classification changes in radiologists. **Key finding:** Radiologists appear to adapt to the images they are inspecting, which could impact perception and may be a source of sequential effects found in batch reading. **Impact on screening strategies:** Visual adaptation effects could potentially be leveraged to improve radiologists' performance by ordering cases in batches by density or other textural properties.

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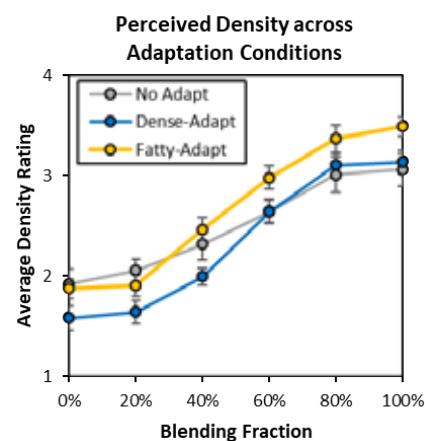


**Figure 1.** Density ratings show effects of different adaptation conditions.

## Association of Acculturation Measures with Mammographic Risk Factors in Latinas

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**Introduction:** Migrant studies indicate that breast cancer (BC) risk increases for women who move from countries with low incidence rates to those with higher rates (e.g., the US)<sup>1,2</sup>. This suggests that acculturation (e.g., changing beliefs or adopting lifestyle practices) and environmental factors increase BC risk among migrant women, but whether these increases are reflected by higher mammographic breast density (MD) and AI-based BC risk estimated from mammograms, is unknown. **Objectives:** This study investigated associations between acculturation measures, genetic ancestry, MD and AI-based breast cancer risk in Latina women. We hypothesized that Latina women who speak English as primary language, were born in the US, and have lived in the US for longer periods would have higher MD and AI-risk. **Methods:** We studied 812 Latina women aged 36-79 years old without prior BC, who had digital screening mammograms performed at a Federally Qualified Health Center in Phoenix, AZ<sup>3</sup>. Acculturation measures were assessed via interview and included primary language spoken (English/Spanish/Both Equally), birthplace (Mexico/US/Other) and years lived in the U.S (<15, 15-20, >20 years). Continental genetic ancestry proportions were estimated from genome-wide genotype data using ADMIXTURE. Mammographic measures included average percent MD from left and right craniocaudal views estimated using LIBRA4, and AI-based 5-year BC risk (MIRAI5) assessed from all views. We used multivariable linear regression models to evaluate associations between acculturation factors, genetic ancestry proportions and their combinations with MD and AI-risk. **Results:** Most women were under age 55 (75%) and overweight or obese (83%). Average percent MD was 18.6% and 5-year AI-risk was 1.9%. After adjusting for age and BMI, women who indicated equal preference for Spanish and English had the highest average density (13.7%), followed by women who preferred Spanish as primary language (10.0%) and those who preferred English (7.7%), with language preference being statistically significant ( $p < 0.05$ ) in models adjusting for age and BMI at time of mammogram. No association was seen between language preference and 5-year AI-risk. Birth location and time lived in the U.S. were not associated with either percent MD or AI-risk. Higher proportion of Native American ancestry showed a positive association with MD ( $p = 0.01$ ), but no association with AI-risk ( $p = 0.12$ ) (Table). Adjusting acculturation associations for genetic ancestry had no impact. **Conclusion:** Our findings regarding acculturation measures were contrary to expected associations with MD and 5-year BC-risk. These results may be due to the younger cohort with high obesity rates or suggest that acculturation measures influence BC risk through other pathways. **Key finding:** Future studies should evaluate differences in acculturation and BC risk factors by birth cohort, education and BMI. **Impact on Screening Strategies:** No direct impact.

Table. Native American Ancestry Association with MD and AI 5-Yr BC Risk

| Proportion Native American ancestry | N   | %   | Mean Percent MD (95% CI) | Mean 5-Yr AI-based Risk (95% CI) |
|-------------------------------------|-----|-----|--------------------------|----------------------------------|
| < 60%                               | 163 | 20% | 9.4 (7.89, 11.26)        | 1.64 (1.53, 1.76)                |
| 60 to 74%                           | 206 | 26% | 9.7 (8.26, 11.30)        | 1.62 (1.52, 1.72)                |
| 75 to 90%                           | 173 | 21% | 10.1 (8.54, 12.03)       | 1.70 (1.59, 1.82)                |
| > 90%                               | 270 | 33% | 10.6 (9.23, 12.15)       | 1.60 (1.51, 1.68)                |
| *All means adjusted for age         |     |     |                          |                                  |

**References:** (1) John E et al. Cancer Epi Biomarkers Prevention. 2005; 12(2905-2913). (2) Tehranifar P et al. Cancer Epi Biomarkers Prevention. 2018; 5(566-574). Shaibi G et al. Public Health Genomics. 2016;19(4):229-38. (4) Gastouniotti A et al. Radiology. 2020; 296(1):24-31. (5) Yala A et al. J Clin Oncol. 2022; 40(16):1732-1740.

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## Fairness In AI-Based Mammography Screening: A Multi-Region Preliminary Study

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**Introduction:** Artificial Intelligence (AI) is already revolutionizing mammography screening. AI has been implemented as an independent reader in at least one hospital in Sweden [1]. Its potential expands beyond detection to risk assessment. However, it is unclear whether AI will decrease or increase ethnic disparities in how early cancer is diagnosed. **Objectives:** Our study focuses on disparities between ethnic groups in terms of exam-level cancer detection (CAD) scores from commercial AI systems – for detection at diagnosis; and risk prediction one to four years prior. **Methods:** The study population consisted of 15056 screening participants, diagnosed with breast cancer, corresponding to 25316 screening exams collected from four regions in Sweden between 2008-2016. The main selection criteria were the availability of a) a screening exam within 4.5 years before diagnosis, and b) registry information on parents' birthplace. We counted each exam twice – one for each parent. Birth countries were grouped into five ancestral ethnic groups: *Sweden* (11241 patients/38086 exams), *Africa* (108/358), *America* (179/598), *Asia* (625/1928), *Europe (not Sweden)* (2597/8684) – and *N/A or Other* (306/978). Each exam was assessed by three commercial AI models that provided a CAD score between 0.000-1.000. We calculated descriptive statistics and quantile-quantile plots to identify the distribution of AI model scores between ethnicities at diagnosis and up to four years before. Mann-Whitney U-Test determined differences with  $p < 0.05$  as statistically significant. **Results:** Figure 1 shows the AI CAD score for AI 1 at different time points. At the time of diagnosis, year 0, the AI CAD score was lower for *America* (0.674; 95%CI: 0.625-0.723),  $p = 0.0002$ , compared to Sweden (0.751; 95%CI: 0.745-0.756). Two years before diagnosis, the AI CAD score was lower for *Asia* (0.191; 95% CI: 0.166-0.216)  $p = 0.0055$  compared to Sweden (0.231; 95%CI: 0.225-0.236), while four years before diagnosis, the score was also lower for *Asia* (0.092; 95% CI: 0.075-0.109)  $p = 0.0003$  compared to Sweden (0.136; 95%CI: 0.132-0.141). All three AI models performed similarly across studied ethnicities. **Key Findings:** We observed some differences in AI CAD scores between ethnic groups at detection (0 years) and risk prediction (1-4 years). Lower scores for Asian ethnicity at prediction points are especially concerning given that already before the use of AI the prognosis for Asians was worse than patients from western countries. **Impact on Screening Strategies:** As AI becomes integral to mammography screening, it is crucial to consider how a single cut-off score threshold might worsen existing ethnic bias in breast cancer prognosis.

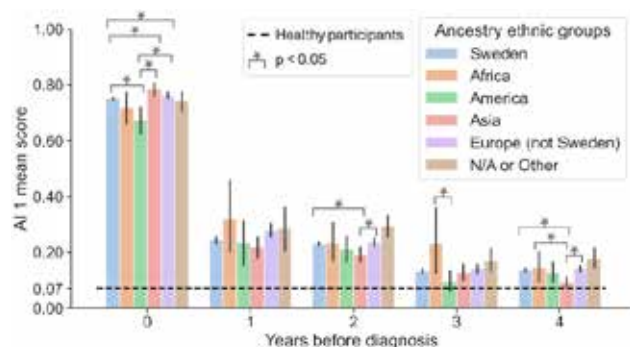


Figure 1: Mean scores (with 95% confidence intervals) for one AI model (AI 1) across ethnicities and time (rounded).

(1) Dembrower, K.; et al. Artificial intelligence for breast cancer detection in screening mammography in Sweden: a prospective, population-based, paired-reader, non-inferiority study. *The Lancet Digital Health*. 2023 Sep 8.

## Association of genetic predisposition genes with breast density and breast cancer risk

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**Introduction:** Breast density and pathogenic variants (PVs) in cancer predisposition genes are associated with increased risk of breast cancer (BC), yet little is known about the association between them.

**Objectives:** We investigated the association between PVs in 5 well-established BC predisposition genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) and breast density, and whether breast density modifies the BC risk associated with PVs. **Methods:** Study participants included women with BC (cases) and unaffected controls from either the CARRIERS consortium or the Mayo Clinic biobank. Breast density data were available as mammographic percent density (PD) and/or clinical BI-RADS (a-d). Using DNA sequencing, loss of function and missense variants labeled as pathogenic or likely pathogenic by ClinVar were classified as PVs. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for binary outcomes. Linear regression was used to estimate least square means for continuous outcomes. All models were adjusted for age and study; BMI was included in the model where breast density was the outcome. **Results:** The study included 4,408 cases and 15,680 controls, with median ages of 57 and 58 years, respectively. The median PD for cases was 26.4% (adjusted for age and BMI), with 38.1% having dense breasts (BI-RADS c/d). The median PD for controls was 20.9% (adjusted for age and BMI), with 33.3% having dense breasts (BI-RADS c/d). *ATM* carriers were less likely than non-carriers to have dense breasts as measured by BI-RADS (OR=0.58; 95%CI: 0.35-0.97) and PD (*ATM* carriers mean PD=19.2%, 95%CI: 16.8-21.7; non-carriers mean PD=22.0%, 95%CI: 21.7-22.4). There was suggestive evidence of lower density in *BRCA1* carriers when assessed by BI-RADS (OR=0.59; 95%CI: 0.33-1.05), but not by PD. There was no evidence of an association between PVs in *BRCA2*, *CHEK2*, or *PALB2* with either BI-RADS or PD. When investigating whether breast density modifies the risk associated with PVs, models including breast density (BI-RADS or PD) yielded similar risk estimates for each gene compared to models not adjusting for density measures (e.g. for *BRCA2*, 7.3-fold increased risk when including BI-RADS vs 6.9-fold excluding BI-RADS in the model). **Conclusion:** There is little evidence to support an association between breast density with PVs in 5 BC predisposition genes, except for *ATM* which was associated with less dense breasts. Breast density does not appear to modify the risk of BC associated with PVs.

**Key finding:** Breast density and PVs in 5 BC predisposition genes may be independent risk factors for BC and both should be included in risk prediction models.

## Assessing the Acceptability of Risk Based Screening in Women with Dense and Non-Dense Breasts Among a Socially Diverse Cohort in New York City

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**Introduction:** Risk-based screening (RBS) that tailors screening frequency based on individual risk may improve the balance of benefits and harms. Previous studies, primarily outside the U.S., assess overall RBS acceptability and more frequent screening, with less focus on less frequent screening and whether acceptability aligns with dense breast (DB) notifications, a widely implemented RBS strategy, and the knowledge supporting DB-based screening (i.e., DB's impact on risk or masking). **Objectives:** We investigated RBS endorsement and acceptability of varying screening frequency by personal risk in diverse women, exploring factors linked to RBS acceptability. **Methods:** We used a follow-up survey (n=239 to date, 2022–2024) within the NYMaDe screening cohort of women aged 40–60 in New York City (70% Hispanic, 11% Black, 69% foreign-born; 40% ≤ high school education). To assess RBS acceptability, we asked: “Would you personally accept having your breast screening [more]/[less] often if found to be at [higher]/[lower] risk of breast cancer?” We classified responses as “Concordant Yes” (accepts both more/less screening), “Concordant No” (accepts neither or only less screening), and “Discordant” (accepts only more screening). Another question assessed overall RBS endorsement. We compared 3-level RBS acceptability by sociodemographics, DB notification eligibility (BI-RADS=C/D from records), and awareness/knowledge of DB's masking or risk effects. **Results:** Most women (70%) were “Discordant,” accepting more screening for higher risk but not less for lower risk. About 15% were “Concordant Yes” or “Concordant No,” and 2.5% accepted reduced screening only. Women with DBs were less likely to accept RBS overall (“Concordant No”: 22% vs. 11%) and less likely “Discordant” (61% vs. 75%). Thirty-six percent had DBs and had been informed of mandatory DB notification. No differences were observed by sociodemographics, first-degree BC family history, or perceived BC risk. RBS endorsement did not differ by awareness or knowledge of DB's impact on BC risk or masking (18% and 28%, respectively). **Conclusion:** Women with DBs are less likely to accept tailored BC screening by risk compared to those without DBs. **Key Findings:** Most women, regardless of breast density, are unwilling to accept less frequent screening for lower risk. Women with DBs were significantly less likely to adjust screening frequency based on risk compared to those without DBs. **Impact on Screening Strategies:** Most women with DBs are otherwise at average BC risk but undergo additional screening due to masking concerns. This highlights challenges to RBS adoption among women with DBs and the need for tailored communication research.

### 3D Vision Transformer Using Digital Breast Tomosynthesis for Breast Cancer Risk Assessment

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**Introduction:** Accurate and individualized breast cancer risk assessment is critical for implementing tailored screening and prevention strategies. Available risk assessment tools, such as the NCI's Gail model, have only modest discriminatory accuracy<sup>1</sup>, and are therefore limited in guiding personalized clinical decisions<sup>2</sup>. Breast screening has transitioned to digital breast tomosynthesis (DBT), and deep learning can be leveraged to capture complex features for risk assessment. **Objectives:** We aim to test the feasibility of a deep learning approach using a vision transformer (ViT) architecture and evaluate its potential to improve breast cancer risk assessment by performing a case-cohort study within the ethnically diverse PennMedicine breast cancer screening cohort. **Methods:** Using a dataset of screening DBT images from 18,584 imaging studies (48% Black women, 48% White women, 4% other), we developed a 3D ViT<sup>3</sup> model to classify future breast cancer using left and right cranio-caudal views. Cases were defined as patients who have developed cancer more than 1 year from screening. The dataset was split into 70/15/15 for training, validation and testing. Images were down sampled in width and high dimensions (512x512), while the number of slices was reduced to 15 central slices. Before the final layer, the learned imaging features were extracted and logistic regression was performed with age, race/ethnicity, BIRADs density, and the extracted imaging feature. **Results:** Our bootstrapped logistic regression model (1000 iterations) demonstrated a pooled AUC, sensitivity, and specificity of 0.656, 0.573, 0.646, respectively in classifying future cancer in the test set (Figure 1). Out of all input features, the predicted probabilities from the ViT model had the highest feature importance followed by age, BIRADs density, then race/ethnicity. **Conclusion:** We performed the first study to date that harnesses the strengths of the transformer architecture to perform breast cancer risk assessment on DBT. By leveraging AI, clinicians may achieve a more precise, personalized approach to risk assessment. Future work will include additional model hyperparameter optimization to improve risk assessment performance and to expand the study to use mediolateral oblique views. **Key finding:** Our work demonstrated feasibility of using a 3D ViT model on screening DBT for breast cancer risk assessment. **Impact on screening strategies:** A deep learning model that can sufficiently explain its decisions will not only gain users' trust, accelerating its clinical translation but could also serve as a valuable discovery tool offering new biological insights into tissue patterns that may drive the development of cancer and therefore pave the way to new risk-reducing interventions. **Acknowledgements:** This work was supported by the 2023 Terri Brodeur Breast Cancer Foundation, the 2023 Komen Career Catalyst Research grant (CCR231010477), and the American Cancer Society—131052-MRSG-17-144-01-CCE.

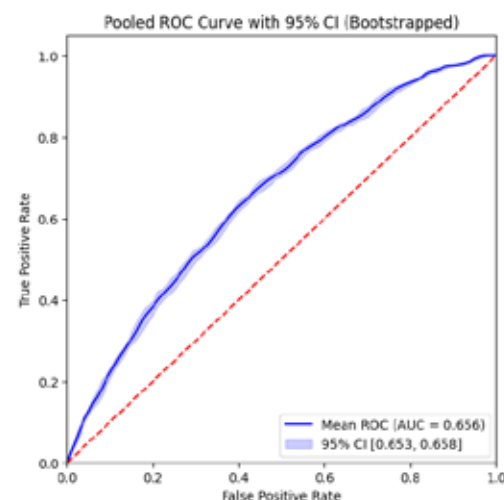


Figure 1. Pooled ROC Curve with 95% CI (bootstrapped).  
Metrics (95% CI low, high)  
TPR: 0.646 (0.635, 0.656)  
TNR: 0.573 (0.549, 0.594)  
AUC: 0.656 (0.653, 0.658)

- (1) Gail MH et al. Journal of the National Cancer Institute 81, 1879-1886 (1989).
- (2) Rockhill B et al. Journal of the National Cancer Institute 93, 358-366 (2001).
- (3) Dosovitskiy A et al. ArXiv 2020 Vol. abs/2010.11929

## Racial/ethnic differences in the performance of radiomic and genomic breast cancer risk prediction models

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**Introduction:** New radiomic and genomic biomarkers can improve the performance of breast cancer risk prediction models. However, new technologies also can exacerbate health disparities due to underrepresentation of minoritized populations in their development and evaluation. **Objectives:** This study evaluates the performance of radiomic and genomic biomarkers for breast cancer risk in a large, diverse population-based cohort. **Methods:** The study population (N=78,098) included 61,962 non-Hispanic White, 7256 Asian, 3414 Black, and 5466 Latina women who enrolled in Kaiser Permanente Research Biobank during 2003-2022 and were screened with full-field digital mammography, and excluded women with a prior history of breast cancer or high-penetrant gene mutation. The Mirai radiomic score was computed for the negative screening mammogram closest to enrollment. An ancestry-adjusted polygenic risk score (PRS) was computed for all women based upon a score with 313 variants developed in European-ancestry women. Ancestry-specific PRS were computed for comparison. We used Cox regression to estimate 10-year breast cancer risk, quantile normalization to account for non-linearity, and 5-fold cross-validation to estimate the concordance index (C-index). **Results:** Incident breast cancers were diagnosed in 2348 women within 10 years following the mammogram, including 1978 White, 177 Asian, 66 Black, and 127 Latina cases. PRS performance was higher in White women (C-index=0.62) than Asian (0.57), Black (0.60), and Latina (0.60) women; results were similar for ancestry-specific PRS with fewer variants. Mirai performance was highest in Latina women (0.70) followed by Asian (0.66), White (0.65), and Black (0.60) women. Addition of ancestry-adjusted PRS to the Breast Cancer Surveillance Consortium (BCSC) v3 clinical risk factor model increased the C-index by 0.04-0.06 in White and Black women, and 0.01-0.03 in Asian and Latina women. Addition of PRS to Mirai increased the C-index by 0.04 in White and Black women and 0.004-0.01 in Asian and Latina women. Addition of both PRS and Mirai to BCSC increased the C-index by 0.06-0.09 in all racial/ethnic groups. **Conclusion:** Larger studies in minoritized populations are needed to close the gap in PRS performance and ensure that performance of radiomic models do not lag behind White women, especially among Black women. **Key finding:** Addition of radiomic and genomic biomarkers substantially improves the performance of clinical breast cancer risk prediction models in all racial/ethnic groups. **Impact on screening strategies:** Implementation of radiomic and genetic testing in the general population can improve personalized risk assessments and increase the benefits while reducing harms of screening mammography.



Figure. Model performance for 10-year breast cancer risk prediction by race/ethnicity.

## Reducing Breast Cancer Screening False Positive Rates using Novel Imaging-Based Models: Opportunities Integrating Quantitative 3-Compartment-Breast Signatures

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**Context:** Over two-thirds of biopsies do not result in a breast cancer diagnosis among women undergoing breast cancer screening in the United States. These false positive screens create an emotional and physical burden that disproportionately impacts women with extremely dense breasts. Models using additional information extracted from screen imaging have the capacity to improve the discrimination of malignant breast lesions and reduce the number of unnecessary breast biopsies. Quantitative 3-compartment-breast (3CB) signatures of lipid/water/protein composition derived from multispectral images are a strong candidate for building new predictive models given differences in these fractions between breast lesions and normal breast tissue.

**Analysis:** When developing new predictive models, the training set plays a critical role in shaping the predictive accuracy among target populations, which we demonstrate using Breast Cancer Screening Consortium data. We show the impact on relative false positive rates for simulated models that either reduce the proportion of false negatives across breast cancer risk groups equally, proportional to risk group representation in the training set, and/or in proportion to the opportunity for improvement. We consider the importance of these training set and model characteristics within the context of model development using 3CB data.

**Key Findings:** Our simulations emphasize the added value of models specifically intended to improve the characterization of lesions in dense breasts and building models using training sets that overrepresent those at high risk of false positives. We contend that the development of 3CB lesion signatures among diverse populations of women is responsive to these needs. We present preliminary data on representation among women recommended for biopsy and recruited to date for a study of 3CB.

**Impact on Screening Strategies:** Our simulations and preliminary results highlight approaches to optimize model performance among those who experience a high burden of false positive screens.

## Performance of breast cancer risk models in a large population-based population

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**Introduction:** Breast cancer risk assessment is increasingly used to guide recommendations for breast cancer screening frequency, supplemental imaging, and prevention. We recently extended the Breast Cancer Surveillance Consortium (BCSC) version 2 (v2) model<sup>1</sup> to include body mass index (BMI), 2<sup>nd</sup>-degree family history of breast cancer, and age at first live birth (version 3 (v3)), but have not compared it with earlier models in an independent cohort.

**Objectives:** To compare the discrimination, calibration, and positive predictive value of the BCSC v3 model to v2 and the Breast Cancer Risk Assessment Tool (BCRAT, aka Gail Model) in an independent population-based screening cohort.

**Methods:** We calculated risk scores for three breast cancer risk assessment tools using publicly available software. We evaluated calibration using the ratio of expected-to-observed (E/O) invasive breast cancers and discrimination using the time-dependent area under the receiver operating characteristic curve estimates (AUROC).

**Results:** We analyzed data from 154,152 women aged 35-79 years without a history of breast cancer. During a mean 10.6 years of follow-up, 5,890 women were diagnosed with invasive breast cancer. The BCSC v3 model had an AUROC of 0.59 for 5-year risk and 0.58 for 10-year risk. Comparisons of the AUROC and the true positive rate (>3% 5-year risk) with both the v2 model and the BCRAT will be presented at the meeting overall and by subgroups including race/ethnicity and BMI.

**Conclusion:** The BCSC v3 model updates an already well-calibrated and validated breast cancer risk assessment tool to include additional important risk factors.

**Key finding:** This is the first validation of the BCSC v3 model in an independent cohort and the first comparison with other widely used models.

**Impact on screening strategies:** Breast cancer screening strategies are increasingly incorporating risk assessment into their recommendations for the starting age of screening and interventions for prevention. Improvements in the BCSC model can advance recommendations for screening and prevention.

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# Mammography AI risk score performance stratified across BI-RADS breast density among a cohort of 183,441 women with a negative screening mammogram from Kaiser Permanente Northern California

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**Introduction:** BI-RADS breast density and mammographic AI are both breast cancer risk factors, but the relative performance of each alone and in combination is not well studied. **Objectives:** Compare performance of BI-RADS breast density and Mirai, a mammography AI risk model, in predicting breast cancer occurrence after a negative screening mammogram in a large and diverse Kaiser Permanente Northern California cohort. **Methods:** Negative screening full-field digital mammograms and BI-RADS assessments from 183,441 women without observable breast cancer history or high-penetrant gene mutation were drawn from the Kaiser Permanente Northern California medical system from 2003-2022. 5-year Mirai risk scores were generated from 4 standard mammographic views. The ability to predict invasive and DCIS breast cancer for three models (BI-RADS, Mirai, and BI-RADS + Mirai) was estimated using a 1000 bootstrap, 5-fold cross-validated Cox proportional-hazards model at various time thresholds using the time-dependent area under the receiver-operator curve and restricted cubic splines for continuous measures in the combined model. Mirai performance alone was further stratified by BI-RADS density. Relative sensitivity of BI-RADS density D and Mirai were compared directly by evaluating Mirai at the threshold corresponding to the number of women classified with density D. **Results:** 6,998 of the 183,441 women developed breast cancer within 15 years. AUCs for BI-RADS, Mirai, and the combined models were 0.59 (0.58-0.61), 0.70 (0.69-0.72), 0.71 (0.70-0.73) at 2 years, and 0.54 (0.53-0.54), 0.67 (0.66-0.67), 0.67 (0.66-0.68) at 10 years. Table 1 reports Mirai performance stratified by BI-RADS density. Comparing sensitivity of density D (7% of women) vs. top 7% of Mirai scores, density D predicted 11% of cancers vs. Mirai predicted 27% at 2 years with 2% overlap, and density D predicted 8% of cancers vs. Mirai predicted 18% at 10 years with 2% overlap. **Conclusion:** Mirai had higher discrimination than BI-RADS breast density for short and long time horizons, with no improvement in the combined model. Mirai alone performed better in density A women at 2 years, but otherwise performed similarly when stratified by breast density and time horizons. Mirai scores detected double the cancers as the same proportion of density D women, with low overlap between the two measures. **Key finding:** Although Mirai is superior to BI-RADS breast density at risk stratification, each risk factor predicts independent cancers, suggesting more sophisticated modeling efforts may improve performance. **Impact on screening strategies:** AI improves risk stratification for supplemental imaging and screening frequency beyond breast density.

**Table 1.** Mirai time-varying AUC(t) and 95% confidence intervals, stratified by BI-RADS breast density at various time horizons

| BI-RADS (% pop.) | 0-2 years            | 0-5 years            | 0-10 years           | 0-15 years           |
|------------------|----------------------|----------------------|----------------------|----------------------|
| <b>A (10%)</b>   | 0.76<br>(0.68, 0.82) | 0.69<br>(0.65, 0.73) | 0.62<br>(0.58, 0.66) | 0.67<br>(0.64, 0.70) |
| <b>B (44%)</b>   | 0.70<br>(0.67, 0.73) | 0.67<br>(0.65, 0.68) | 0.63<br>(0.61, 0.65) | 0.66<br>(0.65, 0.67) |
| <b>C (39%)</b>   | 0.69<br>(0.67, 0.71) | 0.68<br>(0.66, 0.69) | 0.63<br>(0.61, 0.64) | 0.66<br>(0.65, 0.67) |
| <b>D (7%)</b>    | 0.65<br>(0.60, 0.69) | 0.65<br>(0.62, 0.69) | 0.62<br>(0.58, 0.66) | 0.65<br>(0.62, 0.67) |

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