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Personalized breast cancer screening in a population-based study: Women Informed to Screen Depending On Measures of Risk (WISDOM)

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WISDOM Study

In the United States, the majority of women are currently recommended to undergo annual mammographic screening for breast cancer starting at the age of 40, regardless of personal risk. Advances in our understanding of breast cancer biology and screening have led to proposals to update screening guidelines.[1] Despite the recent U.S. Preventative Services Task Force's changes to the guidelines based on review of scientific literature, these recommendations continue to spark debate around the effectiveness of annual screening.

The WISDOM Study is a web-based, preference-tolerant, pragmatic trial comparing traditional annual screening to personalized risk-based breast screening. The WISDOM risk-based paradigm employs a comprehensive risk prediction model incorporating previously established and recently validated genetic and clinical breast cancer risk factors, including mutations in 9 genes (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, ATM, PALB2, and CHEK2), 228 common genetic variants (SNPs), mammographic density, and co-morbidities.[2] 5-year risk of developing breast cancer is calculated according to the Breast Cancer Surveillance Consortium (BCSC) model. For participants in the personalized arm, the 5-year risk BCSC score is combined with a Polygenic Risk Score (PRS).[3] Risk stratification guides age to start/stop, timing, frequency, and modality of screening.).[4] The study is registered on ClinicalTrials.gov as NCT02620852.

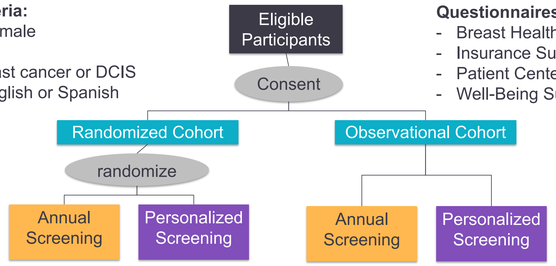
Study Aims

Determine if personalized screening (as compared to annual screening):

1. **Is as safe**
2. **Is less morbid**
3. **Is more accepted by women**
4. **Enables reducing break cancer risk**
5. **Has greater healthcare value**

Study Design

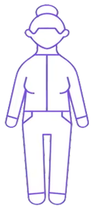
Eligibility Criteria:
- Identify as female
- Age 40-74
- No prior breast cancer or DCIS
- Can read English or Spanish



Questionnaires:
- Breast Health Questionnaire
- Insurance Survey
- Patient Centered Outcomes
- Well-Being Survey (50-74)

Any participant who tests positive for a genetic mutation or is at elevated risk will receive a Breast Health Specialist (BHS) consultation at no cost.

Personalized Breast Screening



Mammogram
Breast Health Questionnaire
Genetic Test BRCA1, BRCA,2, TP53, PTEN, STK11, CDH1, ATM, PALB2, CHEK2, SNPs panel

BCSC
Age
Race/ethnicity
Family history
Prior biopsy
BIRADS density score

PRS
Polygenic Risk Score
Gene mutations

BCSC-PRS
Personalized screening recommendation

Personalized Arm Recommendation are based on age, risk level and mutation status:

Recommendation	Age 40-49	Age 50-74
No screening at this time	5-year risk < 1.3%*	5-year risk < 1.3%* OR 5-year risk < 2.2%, 50%-mortality
Biennial mammogram	5-year risk ≥1.3% AND below top 2.5% distribution by age (BCSC+PRS < 97.5th percentile)	5-year risk below top 2.5% distribution by age (BCSC+PRS < 97.5th percentile)
Annual Mammogram	Extremely dense breasts (BIRADS="D")	-
Annual mammogram + consultation	Top 2.5% distribution by age (BCSC + PRS > 97.5%) OR ATM, or CHEK2 mutation	
Annual mammogram + annual MRI + consultation	5-year risk ≥ 6% OR BRCA 1/2, TP53, PTEN, PALB2, STK11, CDH1 mutation OR History of chest wall radiation received before age 35	

*average risk of a 50-year-old woman
**average risk of a BRCA carrier

Estimated Risk Distribution Personalized Arm:

	Age 40-49	Age 50-74
No screening at this time	75%	5%
Biennial mammogram	11%	91%
Annual mammogram	13%	2%
Annual mammogram + adjunctive MRI	1%	2%

Major reduction in screening compared to annual

Moderate or Elevated Risk

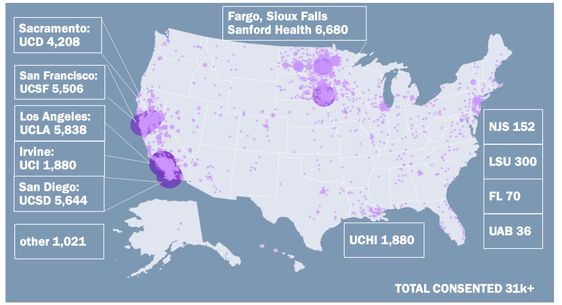
Shieh et al. (2017)

Advocate Statement

It's about time that breast cancer detection finally enters the 21st century so all women can benefit from precision breast health aka right-sized breast cancer screening.
Our goal as advocates is for every woman in the US to know her breast cancer risk so she can:
1) screen appropriately, with high-risk women screening more often with the right modality and low risk women avoiding the harms of too-frequent screening such as false positives and biopsies for inconsequential lesions, and
2) take currently-available measures to lower that risk, if it's high.
Know your risk, reduce your risk! WISDOM will get us there.

Nationwide Enrollment and Diversity

The WISDOM Study is open to women across the United States in English and in Spanish.
Partners: Blue Cross Blue Shield Association for national coverage and engaging with self-insured companies (i.e. Salesforce, Genentech, Qualcomm, CalPERS, UC Health Plans, Health Net Blue and Gold) and Medi-Cal (Inland Health Empire Plan) using a coverage with evidence progression approach.



R01 awarded to increase diversity of enrolled population.
A new WISDOM Community Outreach Board has been set up to reach diverse populations.

As of November 5th 2020:
42,568 registered
31,611 consented
25,822 enrolled
(see map)

Our participants identify as:
0.4% American Indian or Alaska Native
5.1% Asian
2.3% Black/African-American
4.6% Multi-racial
0.2% Native Hawaiian or Other Pacific Islander
2.4 % Some other race
1.1% Unknown
84 % White

Ethnicity:
9% Hispanic
90% non-Hispanic
1% Other

Share Your WISDOM

Join the WISDOM study by visiting our website: www.thewisdomstudy.org
Phone: 855-729-2844
Email: info@wisdomstudy.org

References

1. Esserman et al., The Lancet Onc (2014)
2. Shieh et al., JNCI J Natl Cancer Inst (2017)
3. Shieh et al., Breast Cancer Res Treat (2016)
4. Esserman et al., Nature Breast Cancer (2017)

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