Personalizing Cancer Screening and Prevention Decision Making within the WISDOM Study

Laura J. Esserman, MD, MBA
Professor of Surgery and Radiology
Director, UCSF Carol Franc Buck Breast Care Center

athena

Wisdom

Agenda

- Why we need new approaches in screening
    - One size is not likely to fit all
    - Prevention and screening should be an integrated process
- How trial design can integrate both randomization and preference
    - How can you use shared decision making to get participation in a trial?
- Importance of shared decision making in the high risk/prevention setting
- Stakeholder process, starting before accrual
    - Road test endpoints and impact on adoption
    - Review results
- Engagement of payors in the generation of evidence
- Importance of diversity to improve applicability of results

Wisdom

Breast Cancer Screening Today

- Mired in controversy
- Based on data that is 30+-years-old
- Age-based
- Low risk women are over-screened
  - false positive recalls and benign biopsies
- High-risk women are under-screened missing lethal tumors
- Catchy Public Health Messages miss the complexity
  - “Mammograms Save Lives” and “Early Detection Saves Lives”
- Resource intensive in aggregate: $8 - $10 billion annually

Wisdom

Years of Policy Controversy & Conflict

WISDOM will provide data required to inform professional societies and resolve discordant recommendations

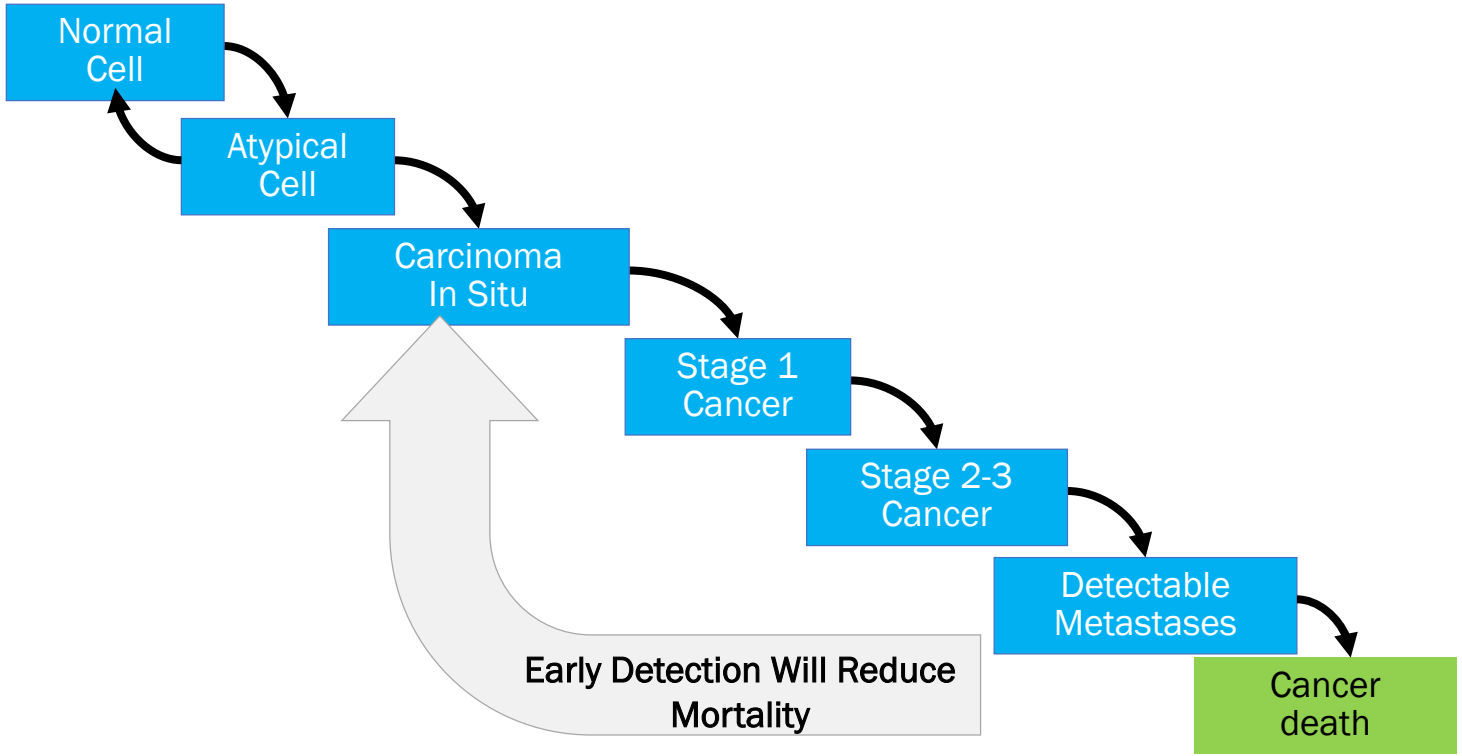
Professional Society	Screening Age	Frequency
USPSTF	40 – 49 50 – 74	Shared decision on whether to screen Biennially (for avg. risk)
ACS	45 – 55 55 – until life expectancy < 10 yrs.	Annually Biennially
ACR / SBI	40 – until life expectancy < 5-7 yrs.	Annually
NCCN	40 – until life expectancy < 10 yrs.	Annually
ACOG	40 – 49 50 – 74	Shared decision on whether to screen Shared decision: Annual or biennial
ACP (new: April 2019)	40 – 49 50 – 74	Shared decision on whether to screen Biennially

Wisdom

How Do You Motivate Patients to Participate in a Trial?

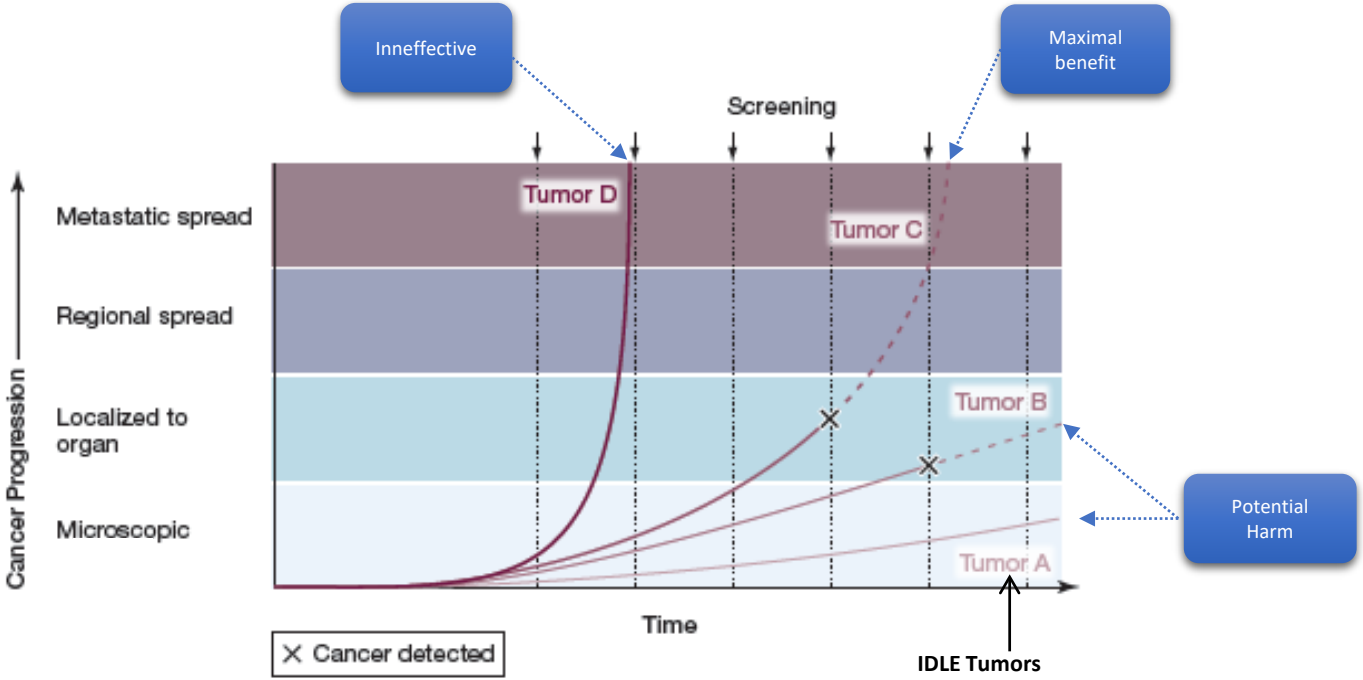
How do you get all of the stakeholders to come together to participate in a trial?

Old Paradigm



New Paradigm: Breast Cancer is not a single disease

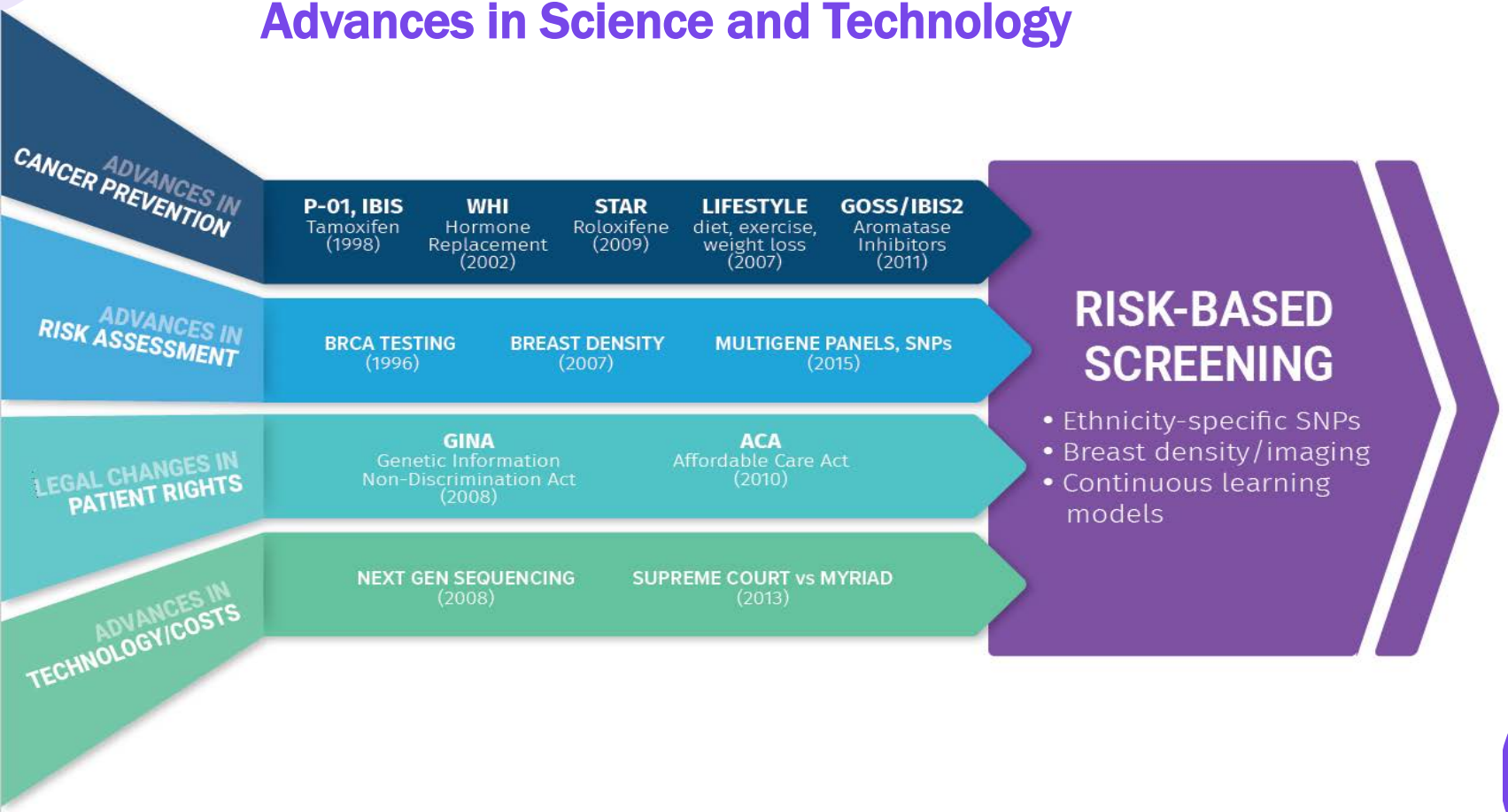
Tumor progression and Benefit (lack of) from Screening



Screening should reflect our new understanding of breast cancer biology

Wisdom

Unprecedented Opportunity: Advances in Science and Technology



“It May Be that One Size Does NOT Fit All for Screening”

Wisdom

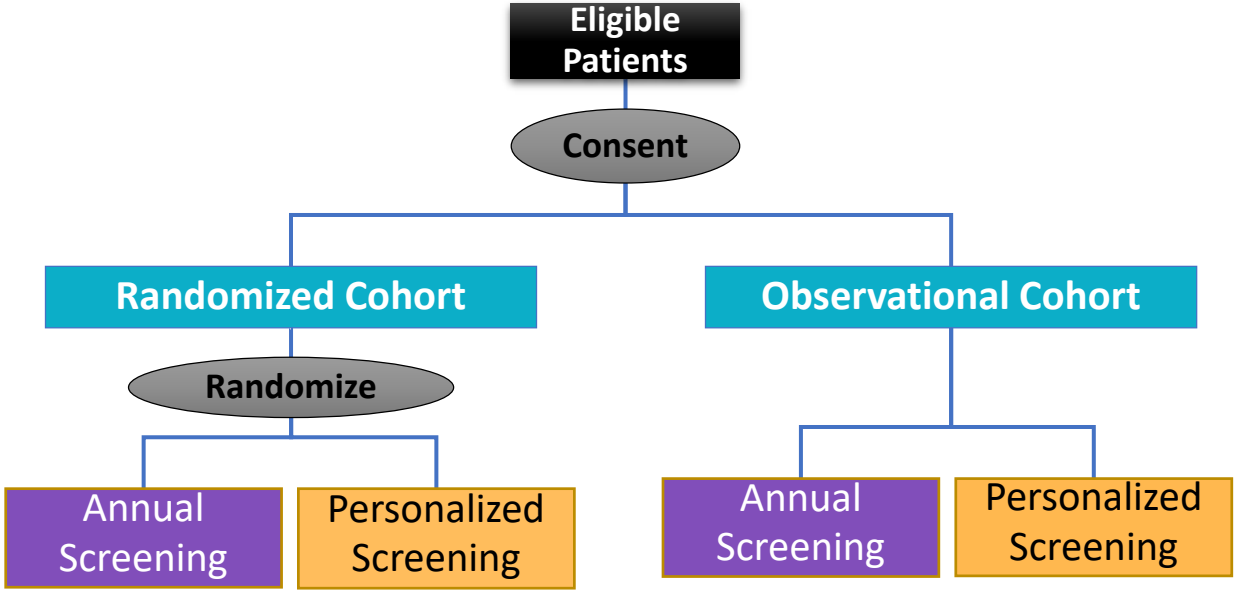
What Breast Cancer Screening Could Be: Personalized and Integrated with Prevention

- Leverages advances in:
  - Biology of breast cancer
  - Risk-assessment
  - Genetics
- More effective at finding “clinically meaningful” cancers
- Personalized and precise for each individual woman
- Integrated with risk reduction strategies
- More cost-effective

How do you get women to participate in a randomized trial?

Wisdom

Pragmatic Trial Design: Preference Tolerant RCT

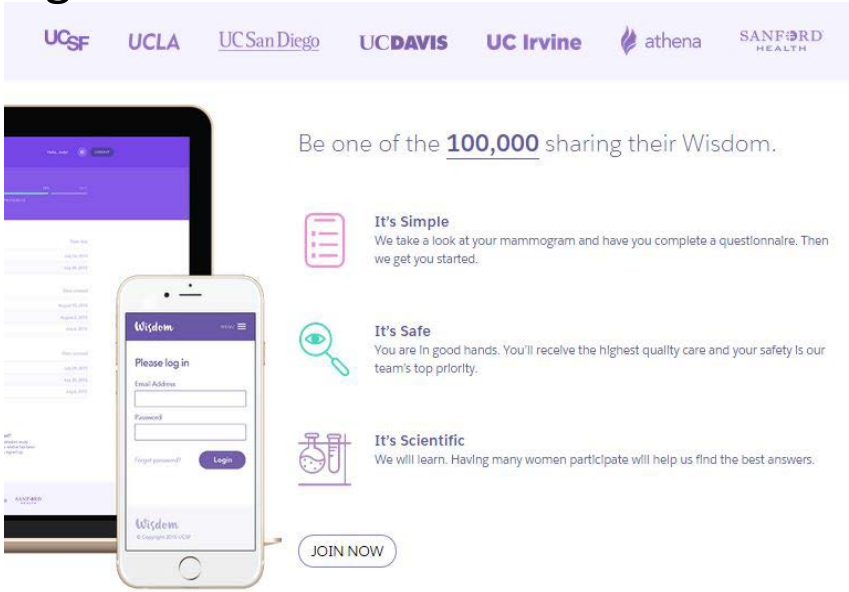


Most women spend 30-35 years screening. Why not spend the next 5 years with us and help us get better answers about how best to screen?

Wisdom

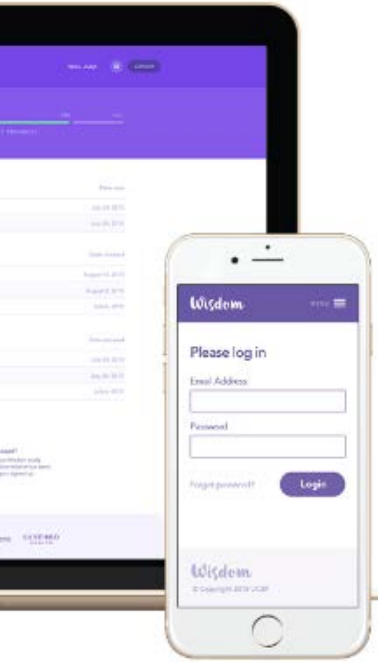
Comprehensive risk prediction model

- Validated high-impact risk factors including
  - Exposures/Lifestyle
  - Breast density
  - 9 breast cancer genes
  - SNPs polygenic risk score
    - 76→303 SNPs
- Tailor screening/prevention plans
  - Age to start/stop
  - Frequency
  - Screening modality
  - Risk reduction



Wisdom

Wisdom 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 prevention
5. Has greater health care value

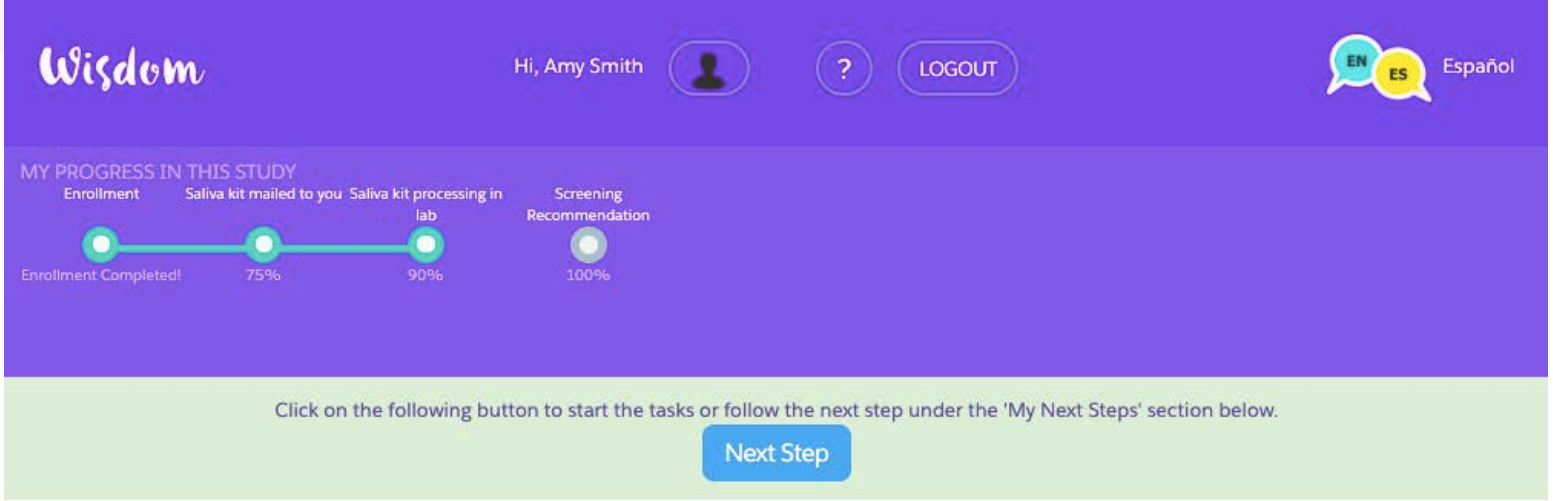
WISDOM Study Structure

- All reporting is automated using the WISDOM platform
- Offered nationwide
  - Recruitment hubs in California, Dakotas, Iowa, Minnesota, Illinois, Alabama, Louisiana

60-65% of women choose randomization

Breast Cancer Screening Trials

- WISDOM
- My PeBS
  - International (7 countries) RCT: Risk based vs. national guidelines
  - Endpoint: detection of stage 2 cancers
  - Sister study to WISDOM, age 40-70, 85,000 women, 2019-2025
  - Uses SNPs, density, exposures(BCSC) for risk assessment (mutations not included)
  - Lowest 20% of risk do not get screened
  - No shared decision making
- T-MIST
  - Digital Tomosynthesis (3D) vs. Digital mammography
  - RCT , Reads out 2030
  - No shared decision making
- DENSE (Netherlands) and Fast MRI vs. 3D (complete)
  - For women with dense breasts, contrast imaging performs better than std mammo, 3D



My Next Steps

Well-being Survey

Thank you for completing your consent and study surveys. You have been assigned to the Personalized group.
You will need to provide a saliva sample to complete your personalized risk assessment. Please look for a new file under 'My Documents' called Personalized Screening - Genetic Testing Instructions to learn more about how to provide a saliva sample. If you do not see the document under 'My Documents' please refresh your screen

Update your profile

Interactive tools

Risk Assessment Tool -Breast Health Decisions

Wisdom

MY BREAST HEALTH DECISION GUIDE ☑

Wisdom

Automated integration of risk education tool

Includes risk factors and interventions to lower risk

Threshold for outreach (personalized arm): Top 2.5 % risk by age group

Breast Health Decisions Tool

My Risk Snapshot

This information comes from your patient profile and your answers to the Breast Health Questionnaire that you completed on 3/19/2019

My age	60
My race	White
My family history of breast cancer	Yes
My breast biopsy history	Benign non-proliferative findings
My breast density	Almost entirely fatty

These calculations are based on your genomics report and your patient profile

Breast Cancer Surveillance Consortium (BCSC) 5-year risk score	1.79%
Polygenic risk score (PRS)	1.60
BCSC + PRS 5-year risk score	2.83%

Understanding the risk factors

What is a breast biopsy?

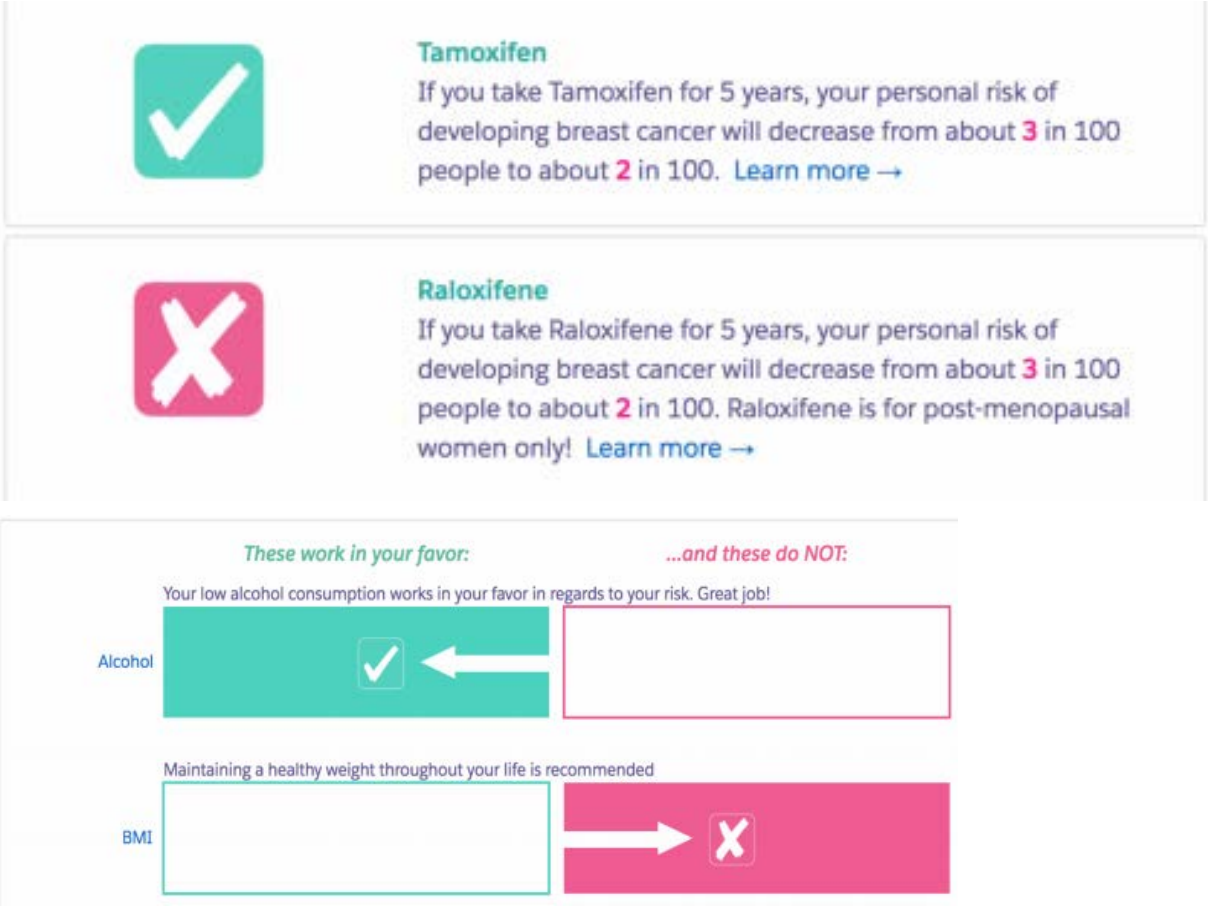
A breast biopsy is when a piece of breast tissue is removed for further study by a pathologist. Breast biopsies are safe, and do not cause cancer.

There are many types of biopsies:

- Core biopsies take fine tissue samples.
- Incisional biopsies take small tissue samples.
- Excisional biopsies take large tissue samples.

Why do previous breast biopsies matter?

Previous breast biopsies may suggest an increased risk of developing breast cancer, especially if a pathologist finds an abnormality like atypia or LCIS


Tamoxifen
If you take Tamoxifen for 5 years, your personal risk of developing breast cancer will decrease from about 3 in 100 people to about 2 in 100. Learn more →
Raloxifene
If you take Raloxifene for 5 years, your personal risk of developing breast cancer will decrease from about 3 in 100 people to about 2 in 100. Raloxifene is for post-menopausal women only! Learn more →
These work in your favor:
...and these do NOT:
Your low alcohol consumption works in your favor in regards to your risk. Great job!
Alcohol
Maintaining a healthy weight throughout your life is recommended
BMI

BHD Tool Pilot Quantitative Results

- 20 had Breast Health Specialist Consult of Tool
  - **14** completed Quantitative Feedback Survey
  - **11** completed Follow Up Interview
- Better understanding of their chance of developing breast cancer:
  - 100% (14 / 14 participants)
  - 93% (13 /14 participants) "extremely helpful" or "very helpful" in helping understand breast cancer risk:
- Consider prevention interventions
  - 71% (10/14 participants) lifestyle changes (exercise, reducing alcohol intake and BMI):
  - 43% (6 /14 participants) Consider chemoprevention:
  - 7% (1 / 14 participants): Consider surgical risk reduction

Std: 3% uptake of chemoprevention when offered or recommended

Wisdom

PCORI Principles

- Results ready in a timely way
  - Used a surrogate endpoint- no increase in stage 2B cancers

- Tests had to be covered by the study (payors participating)
  - Coverage with Evidence Progression model
  - Compared to annual, cost saving over time
  - Champion: Blue Cross Blue Shield and self-insured employers

- Stakeholder Engagement
  - Annual stakeholder meetings to project results
  - All guideline makers, payors, providers at the table

Current Health Plan Participation

- Wisdom clinical services are not covered by PCORI funding
- Pragmatic approach requires results to be ‘shovel-ready’
- Agreements with health plans and self-insured employers required to cover the costs of tests
- Partnered with Blue Shield CA (PPO fully-insured) to enroll beneficiaries across California and then BCBSA for national expansion
- Partnered with self-insured employers:
  - UC Care / Anthem, Salesforce / Aetna, Roche-Genentech / Qualcomm /CalPERS

Cost-Benefit Summary

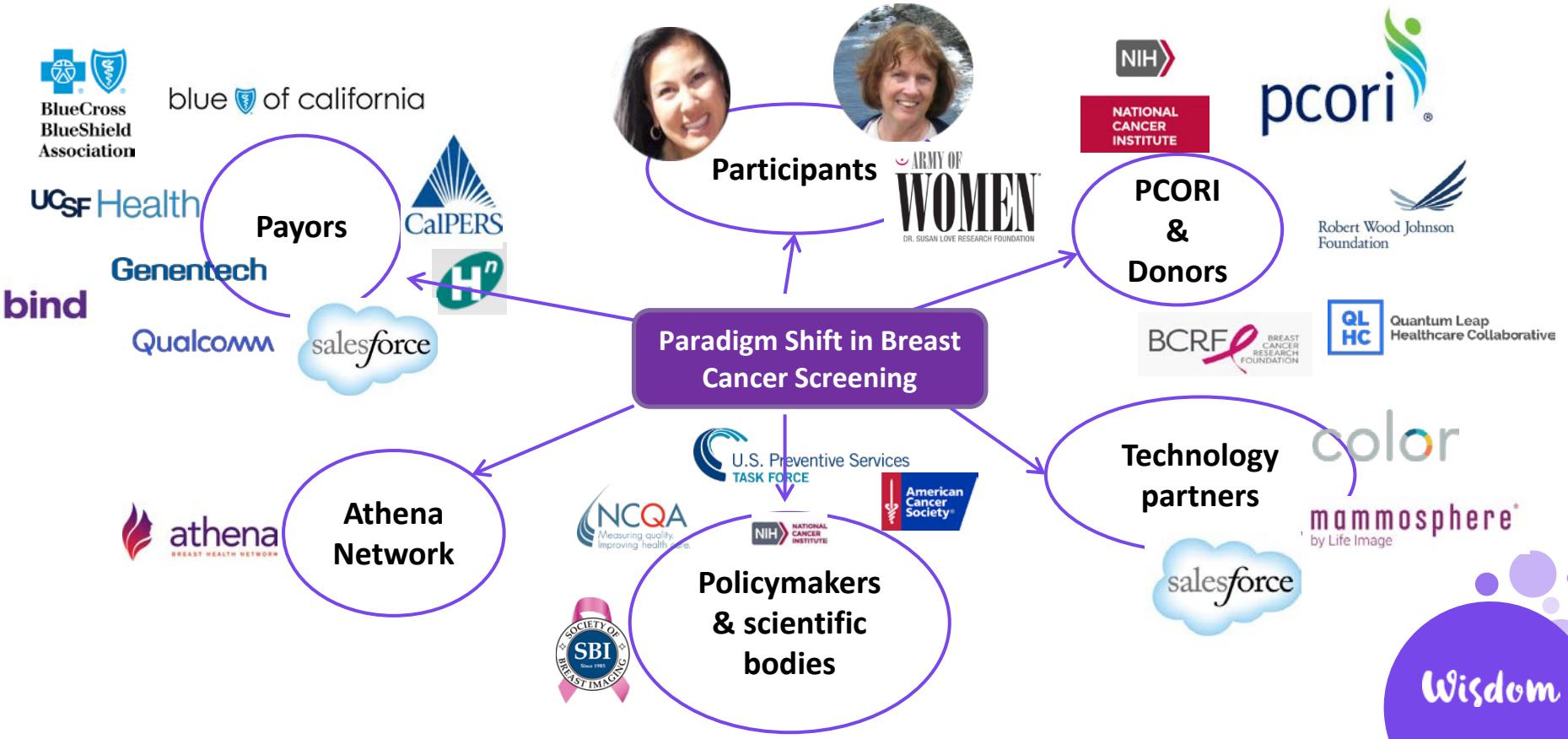
Assumptions: Medicare rates, actual screening rates of every 15 months & 10% plan turnover

- Initial investment of $195 per participant yields **$30 in 5-year savings**
- Participants who remain on the health plan after year 1 provide **$55 in yearly savings**
- Even when considering plan turnover, this results in a **break-even period of 4 years with continual savings thereafter**

Wisdom is at worst cost neutral: Participants that leave the health plan early may result in unrealized savings, but **savings from participants who remain far outweigh the overall investment**

Wisdom

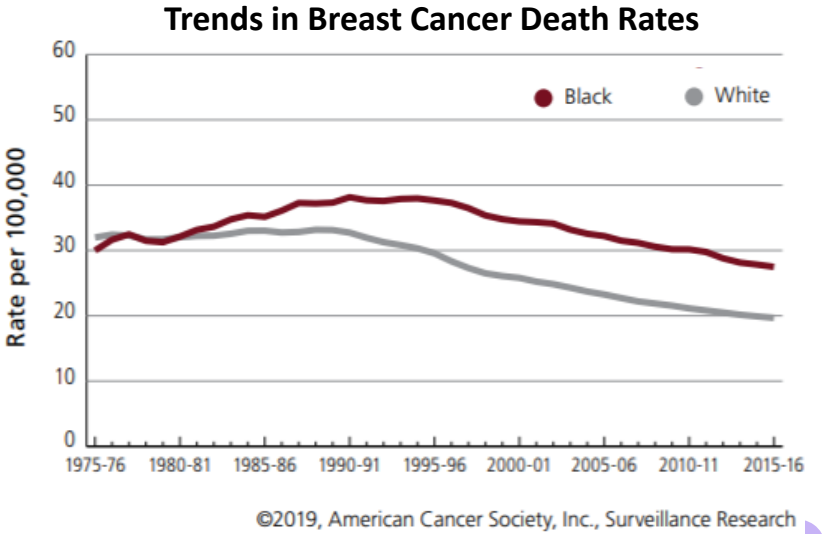
Everyone Benefits if Everyone Participates



Wisdom

Disparities in Incidence and Mortality

- Breast cancer incidence and mortality disparities between Black and White women
- Likely due to differences in tumor biology, genomics and health care delivery patterns
- Huge disparity in access to genomic testing and uptake of risk-reducing interventions
- Urgent need to conduct rigorous research and disseminate effective interventions in order to tailor screening and treatment strategies for every woman



Patient-Centered and Inclusive

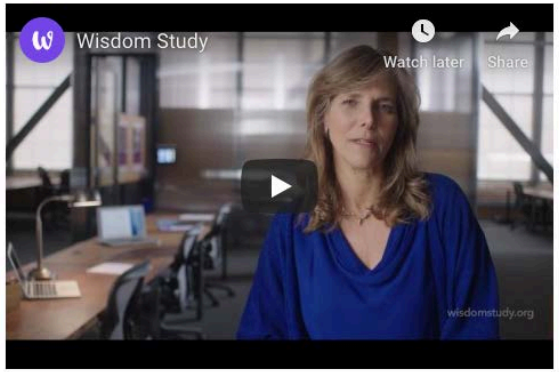
- Spanish Translation
  - Outreach Materials
  - All study communications

- Plain-language translation
  - Materials modified with simpler, 6th grade reading level

Wisdom

WISDOM Attributes

- Use of established tests in new ways
- Coverage with evidence development/progression
- Virtual trial design
  - Trial comes to the participant not vice versa
- Technology platform with embedded analytics
- All stakeholders at the table from beginning
  - reduce time to implement trial results
- Risk model is updated as new data emerges
- Patient Reported Outcomes
- Patient education and risk communication (BHD Tool)
- Bioethics Committee & Embedded Ethics Study
- Profile tumors that arise: learn who gets what kind of cancer
- ***Challenge: Keep women engaged so we can get accurate followup***



Publications

- Nature Reviews (2016): Population-based screening
- Nature Breast (2017): Commentary
- JNCI (2017): Risk Thresholds
- Health Affairs Blog (2017)
- JNCI (2019): WISDOM Statistical approach and simulations
- Nature Perspective (2020): The Only Way to Know Better is to Do Better

Breast Screening Trials (N>1000)

My Personal Breast Screening (MyPeBS): MyPeBS is an international randomized, open-label, multicentric, study assessing the effectiveness of a risk-based breast cancer screening strategy (using clinical risk scores and polymorphisms) compared to standard screening (according to the current national guidelines in each participating country) in detecting stage 2 or higher breast cancers (NCT03672331)

- Interventional, randomized, 2019-2025, N=85,000; Ages 40-70

Digital Tomosynthesis Mammography and Digital Mammography in Screening Patients for Breast Cancer: This randomized phase III trial studies digital tomosynthesis mammography and digital mammography in screening patients for breast cancer. Screening for breast cancer with tomosynthesis mammography may be superior to digital mammography for breast cancer screening and may help reduce the need for additional imaging or treatment (NCT03233191)

- ECOG-ACRIN group
- Interventional, randomized, Phase 3 2017-2030, N=164946; Ages 45-74

Stand up to Cancer: MAGENTA (Making Genetic Testing Accessible): This randomized clinical trial studies how well online genetics educational video with or without pre- and/or post-telephone genetics counseling works in assessing cancer-risk distress in patients with triple negative breast cancer. Online genetic education and telephone genetic counseling may help the doctors learn the stress a person feels about their risk of cancer (NCT02993068)

- MD Anderson, University of Washington
- Interventional, randomized, 2017-2022, N=4000; Ages 30+

Combined Breast MRI and Biomarker Strategies in Identifying High-risk Breast Cancer Patients: This clinical trial studies normal breast tissue changes combined with breast magnetic resonance imaging (MRI) that may suggest the beginnings of cancer development. Using breast tissue markers in combination with breast imaging such as MRI may help to more accurately assess a woman's risk of developing breast cancer (NCT03303846)

- City of Hope
- Single Group assignment, 2017 – 2021, N=650; Ages 18+

MERIT (Mammography, Early Detection Biomarkers, Risk Assessment, and Imaging Technologies) Cohort: The goal of this research study is to create a bank of research samples and a database of clinical and risk information from women undergoing routine screening mammograms, for use in future research related to breast cancer, other cancers, and women's health. This research study will collect mammogram images, blood samples, and clinical information (NCT03408353)

- MD Anderson
- Observational study, 2017 – 2023, N= 10,000; Ages 25 - 80

Breast Cancer Screening With MRI in Women Aged 50-75 Years With Extremely Dense Breast Tissue: the DENSE Trial The purpose of this study is to determine the cost-effectiveness of biennial screening with mammography and MRI compared to mammography alone in women aged 50-75 years and who show > 75% mammographic density. NCT01315015

- Netherlands N Engl J Med 2019; 381:2091-2102
- RCT 2011-2019 N- 36185 participants Women ages 50-75

Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women With Dense Breasts Undergoing Screening Fast MRI vs. 3D mammography to assess sensitivity and specificity of detection of breast cancer in women with moderately and very dense breast

- ACRIN ECOG US and Germany Results reported *JAMA.* 2020;323(8):746-756.
- Women age 40-75, N=1444; Cross sectional study,

Wisdom