



CALIFORNIA TECHNOLOGY
ASSESSMENT FORUMSM

Supplemental Cancer Screening for Women with Dense Breasts

Public Meeting

September 25, 2013

Agenda

- **Meeting Convened** | 10am-10:15am
- **Presentation of the Evidence and Voting Questions, Q&A**
| 10:15am – 11:15am
- **Discussion and Public Comments** | 11:15am – 12:15pm
- **Working Lunch** | 12:15pm – 1pm
- **CTAF Deliberation and Votes** | 1pm – 1:45pm
- **Roundtable Discussion of Best Practice Recommendations**
| 1:45pm – 3:45pm
- **Summary and Closing Remarks** | 3:45pm – 4pm
- **Meeting Adjourned** | 4pm

CTAF

- Funding:
 - Blue Shield of California Foundation
- Goal:
 - To improve the application of evidence to guide practice and policy in California
- Structure:
 - Evidence review from UCSF faculty
 - Deliberation and voting by CTAF Panel: independent clinicians, consumer and patient representatives, and methodologists



CALIFORNIA TECHNOLOGY
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Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue

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September 25, 2013

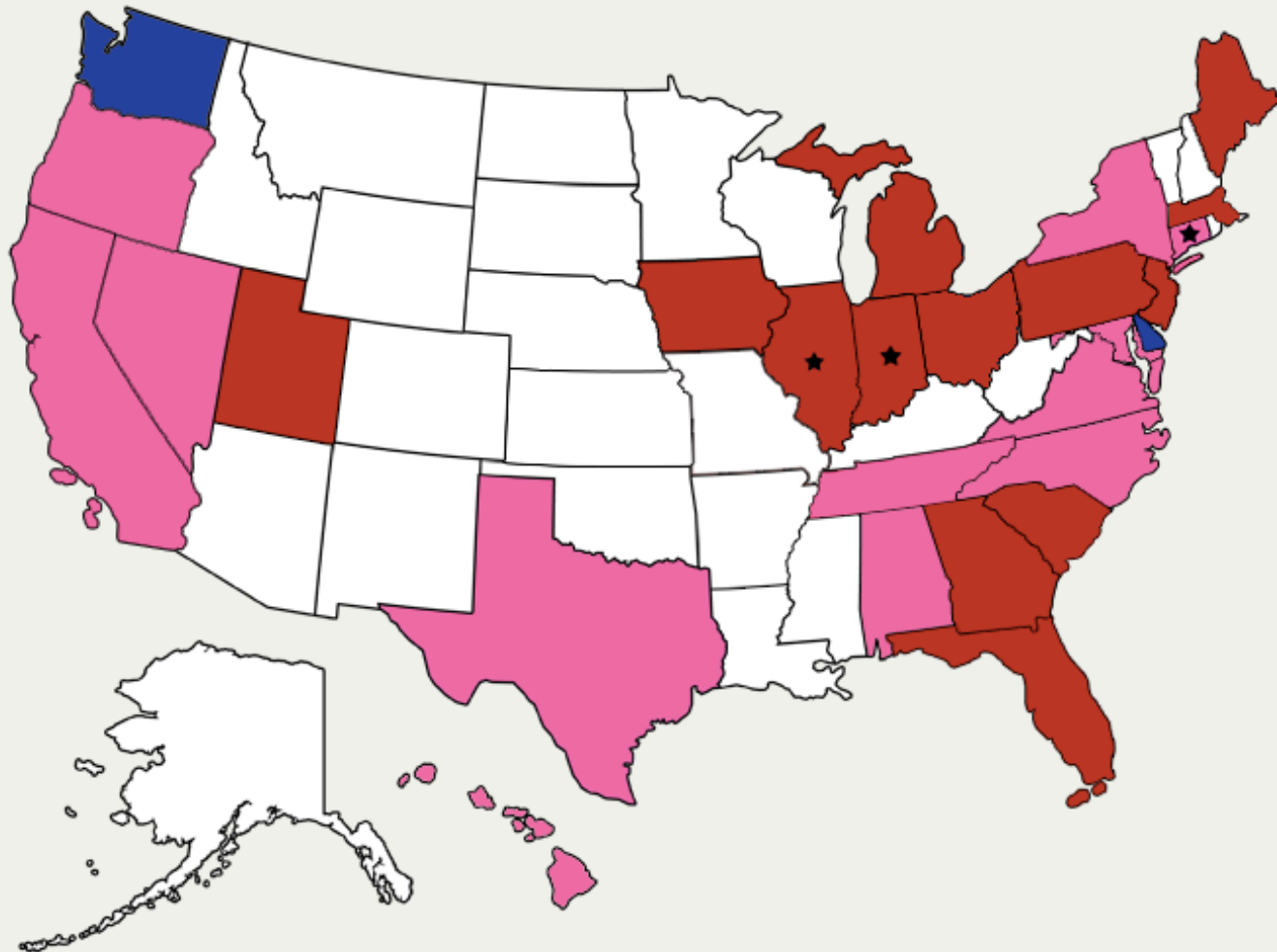
CA SB1538 effective April 1, 2013

Women with dense breasts must receive the following language with their results:

“Your mammogram shows that your breast tissue is dense. Dense breast tissue is common and is not abnormal. However, dense breast tissue can make it harder to evaluate the results of your mammogram and may also be associated with an increased risk of breast cancer. This information about the results of your mammogram is given to you to raise your awareness and to inform your conversations with your doctor. Together, you can decide which screening options are right for you. A report of your results was sent to your physician.”

About D.E.N.S.E.™

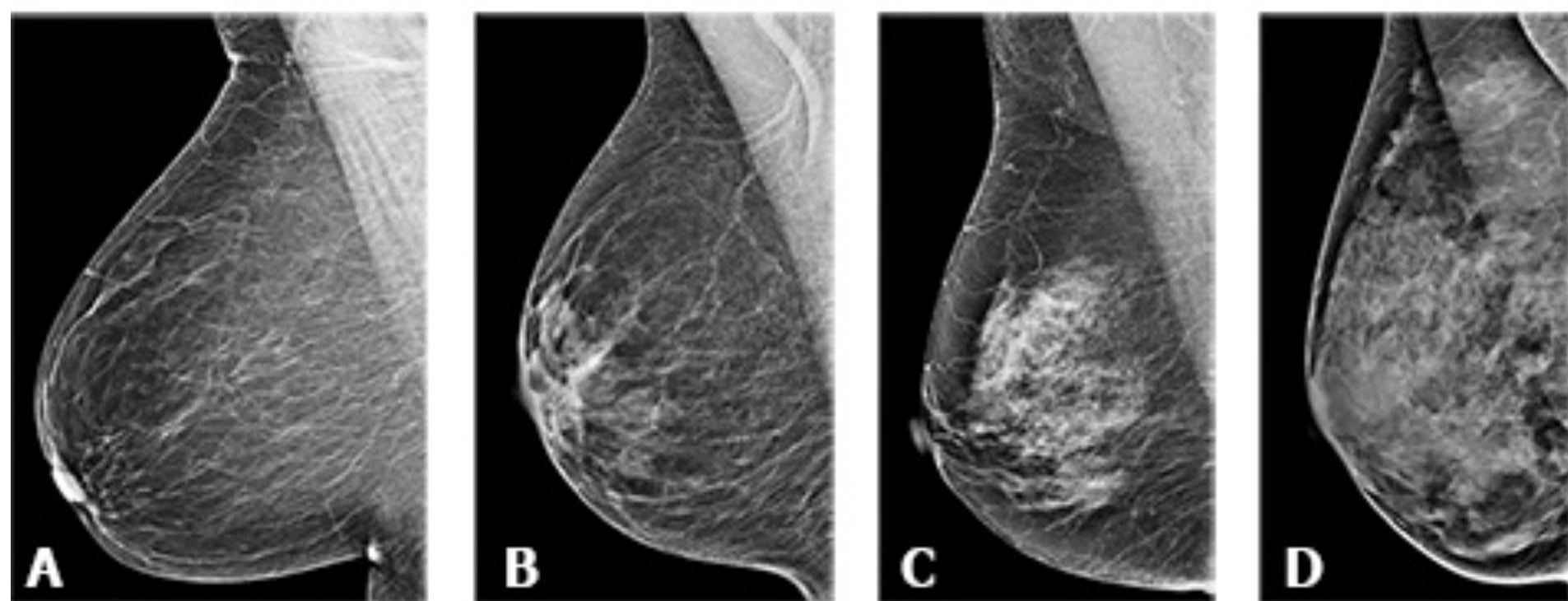
Click on your state to find information about "mandatory breast density notification" legislative efforts.



PINK: Enacted Law — RED: Introduced Bill — BLUE: Working on Bill — WHITE: No Action — BLACK * : Insurance Coverage Law

What is dense breast tissue?

According to BI-RADS®, breast density ranges among (A) an almost entirely fatty breast, (B) a breast with scattered areas of fibroglandular density, (C) a heterogeneously dense breast, and (D) an extremely dense breast.



Definitions

- Sensitivity: % cancers with positive test
- Specificity: % no cancers with negative test
- PPV3: % of biopsies with cancer
- Cancer detection rate: Cancers / 1000 tests
- Recall rate: Recalls / 1000 tests
- Biopsy rate: Biopsies / 1000 tests

Interval cancer: cancers not found on testing that are diagnosed in the subsequent year (365 days)

Breast Density and Masking

| Density | Sensitivity |
|-----------------------|-------------|
| Almost entirely fatty | 88% |
| Scattered densities | 82% |
| Heterogeneously dense | 69% |
| Extremely dense | 62% |

Sensitivity: the number of cancers detected divided by the total number of cancers present (usually those diagnosed within 1 year)

NB ~463,000 film mammograms

Breast Density and Risk

| Density | Relative Risk | Prevalence |
|-----------------------|---------------------|------------|
| Almost entirely fatty | 0.5 | 10% |
| Scattered densities | 1 (reference group) | 40% |
| Heterogeneously dense | 1.5 | 40% |
| Extremely dense | 2.0 | 10% |

Breast Cancer

- Lifetime risk: 12%
- Mortality declining 2.2% per year from 1990 to 2005
 - 28% overall decline
 - Proportion due to mammography screening versus improvements in treatment remains controversial

Mammography screening benefits

- 9 RCTs >600,000 women followed for 10-20 years
- 20% to 25% relative reduction in breast cancer specific mortality
- Absolute risk reduction 0.18% or 1.8 per 1000 women screened with annual mammography over 15 years

Mammography screening harms

- False positive results
 - ~ 10% each round
 - ~ 50% of women after 10 mammograms
 - Time for repeat imaging and breast biopsies
 - Anxiety, decrease in well being
- Overdiagnosis: 10% to 30% of cancer diagnoses
 - Treatment harms with no benefits
- Radiation exposure (~2 months of background)
 - 1,000 women screened 20 times ages 40 to 75 years
 - 0.86 extra breast cancers and 0.11 extra deaths from BC

Digital Mammography (DM)

- Digital replacing film: more than 90% of facilities in 2013
- DMIST Study 2005
 - 42,760 women with both film and digital mammography
 - ~20,000 with dense breast tissue

| Statistic | Film | Digital | P |
|----------------------|------|---------|-------|
| Sensitivity | 55% | 70% | 0.02 |
| Specificity | 90% | 91% | 0.09 |
| Area under ROC curve | 0.68 | 0.78 | 0.003 |

Key Point #1

- Digital mammography improves sensitivity, while preserving specificity, in women with dense breast tissue.

Digital Mammography (DM)

- Breast Cancer Surveillance Consortium
- ~870,000 mammograms at a mix of academic and community practices across the United States

| Density | Sensitivity Film | Sensitivity Digital |
|-----------------------|------------------|---------------------|
| Almost entirely fatty | 86% | 78% |
| Scattered densities | 85% | 87% |
| Heterogeneously dense | 79% | 82% |
| Extremely dense | 68% | 84% |

Key Point #2

- Masking (decrease in sensitivity of mammography) is greatly reduced with digital mammography

Four FDA approved technologies

- Magnetic resonance imaging (MRI)
- Hand held ultrasound (HHUS)
- Automated whole breast ultrasound (ABUS)
- Digital breast tomosynthesis (DBT)

Magnetic resonance imaging (MRI)

- Strong magnetic fields
- Cross-sectional images of the breast: 3D
- Concerns
 - IV – invasive
 - IV contrast – allergic reactions
 - False positive results
 - Time and cost

Hand held ultrasound (HHUS)

- High frequency sound waves guided by hand
- Cross-sectional images of the breast: 3D

- Concerns
 - False positives
 - Operator dependent
 - Real time availability of radiologists
 - Time
 - Inadequate reimbursement

Automated breast ultrasound (ABUS)

- High frequency sound waves guided by computer
- Cross-sectional images of the breast: 3D

- Concerns
 - False positives
 - Limits to breast size that can be imaged
 - Time

Digital breast tomosynthesis (DBT)

- Images of the breast from multiple angles
- Cross-sectional images of the breast: 3D

- Concerns
 - Ionizing radiation = 2nd mammogram
 - Approaches to biopsy when only seen on DBT

MRI as supplemental screening

- Recommended and covered for lifetime risk >20%
 - Targeted at hereditary risk such as BRCA1/2 carriers
- No studies in women based on dense breast tissue
- In high risk women: 11 observational studies
 - High cancer detection rate: ~ 23 per 1000 examinations
 - 2 to 3-fold higher than the CDR for DM and/or HHUS
 - High PPV3: ~ 48%

MRI summary

- High levels of uncertainty – no direct evidence
- 1000 women; dense tissue + negative DM
 - Assume DM found 5 cancers; HHUS would find 3 more
 - MRI (CDR is double that of DM+US)

| Statistic | DM | Added with MRI | Uncertainty |
|----------------------|------|----------------|-------------|
| Recall rate per 1000 | 128 | 100 | High |
| Biopsy rate per 1000 | 17.8 | 17-36 | High |
| CDR per 1000 | 4.2 | 8 | High |
| PPV3 | 24% | 22%-48% | High |

HHUS as supplemental screening

- Best direct evidence: CT experience
 - Hooley 2012; Weigert 2012; Parris 2013
 - Retrospective observational data: poor quality
 - No sensitivity / interval cancer rate
 - Incomplete reporting of recall rate
- Best indirect evidence: ACRIN 6666
 - Berg 2012
 - Prospective, but in a high risk population that included women with non-dense breast tissue

HHUS results

| Study | Recall rate per 1000 | Biopsy rate per 1000 | PPV3 | CDR per 1000 |
|--------------|----------------------|----------------------|------|--------------|
| Hooley 2012 | 56.7 | 56.7 | 5.7 | 3.2 |
| Weigert 2012 | 49.6 | 48.3 | 6.7 | 3.2 |
| Parris 2013 | 33.5 | 32.8 | 5.5 | 1.8 |
| ACRIN 6666 | 185.7 | 88.0 | 6.8 | 5.9 |

HHUS Summary

- Greatest clinical experience / publications
- Low cancer yield per biopsy (PPV3)
- Uncertainty about recall rate

| Statistic | DM | Added with HHUS | Uncertainty |
|----------------------|------|-----------------|--------------|
| Recall rate per 1000 | 128 | 98 | High |
| Biopsy rate per 1000 | 17.8 | 49 | Low-moderate |
| CDR per 1000 | 4.2 | 2-3 | Low |
| PPV3 | 24% | 7% | Low |

ABUS as supplemental screening

- 3 relatively small studies
- Wide variation in results
 - Recall rate 5 to 207 per 1000 examinations
 - Biopsy rate NR, 12, and 15 per 1000 examinations
 - PPV3 NR, 15% and 31%
 - CDR 0 to 7.6 per 1000 examinations

ABUS Summary*

| Statistic | DM | Added with ABUS | Uncertainty |
|----------------------|------|-----------------|-------------|
| Recall rate per 1000 | 128 | 98 | High |
| Biopsy rate per 1000 | 17.8 | 49 | High |
| CDR per 1000 | 4.2 | 2-3 | High |
| PPV3 | 24% | 7% | High |

* Same as HHUS, but high uncertainty for all estimates

DBT as supplemental screening

- No direct evidence
 - 4 studies of concurrent DM + DBT published in 2013
 - Better sensitivity and specificity than DM alone
 - Decreased recalls and false positive results versus DM alone
 - Only Rose 2013 reported biopsy rate and PPV3

| | <u>DM</u> | <u>DM + DBT</u> |
|-------------|-----------|-----------------|
| Biopsy rate | 15.2 | 10.6 |
| PPV3 | 26.5 | 24.7 |
| CDR | 3.9 | 5.4 |

- Only Ciatto 2013 reported data on subgroup with dense breast tissue and a negative DM (next slide)

DBT in dense tissue, negative DM

- Ciatto 2013: Italian Study
 - Recall rate: 21.3 per 1000 examinations
 - Biopsy rate: Not reported
 - PPV3: Not reported
 - CDR: 2.7 per 1000 examinations

DBT Summary

| Statistic | DM | Added with DBT | Uncertainty |
|----------------------|------|----------------|---------------|
| Recall rate per 1000 | 128 | 20 | Moderate-High |
| Biopsy rate per 1000 | 17.8 | 5 | Moderate |
| CDR per 1000 | 4.2 | 1-3 | Moderate |
| PPV3 | 24% | 25% | Low-Moderate |

Key ongoing studies

- RCT MRI+DM versus DM in women with extremely dense breasts
- RCT HHUS+DM versus DM
- RCT ABUS versus DM
- HHUS and DBT in same women with dense breast tissue (think DMIST)
- BCSC: HHUS+DM versus DM in women with dense breasts

Quantitative summary

| Statistic | DM | MRI | HHUS/ABUS | DBT |
|-------------|------|---------|-----------|-----|
| Recall rate | 128 | 100 | 98 | 20 |
| Biopsy rate | 17.8 | 17-36 | 49 | 5 |
| CDR | 4.2 | 8 | 2-3 | 1-3 |
| PPV3 | 24% | 22%-48% | 7% | 25% |

High degree of certainty

- All forms of supplemental screening find additional cancers
- Most of the cancers are small, lymph node negative cancers that are potentially curable
- MRI finds the most cancers (highest sensitivity)
- DBT has few false positives (low recall rate, high specificity)
- HHUS has many false positive biopsies (lowest PPV3 or cancer yield per biopsy)

Overall summary of supplemental screening in dense breast tissue

- No studies with breast cancer survival outcomes
- No high quality studies report the test characteristics for any of the technologies in women with dense breast tissue and a negative mammogram
- MRI: most sensitive; more than doubles the CDR; reasonable PPV³; but most uncertainty
- HHUS: most experience and study data; low PPV³ (7%: many unnecessary biopsies); likely more false positives than reported in published studies.

Overall summary 2

- ABUS: sparse, heterogeneous data. For our analysis anchoring on HHUS results
- DBT: Low false positive rate; low biopsy rate; high PPV3; but no direct data as supplemental screening
- Uncertain about the proportion of cancers detected by supplemental screening that represent
 - Cancers that will be cured because of early detection
 - Cancers that would have been cured if detected later by the patient or through subsequent screening
 - Overdiagnosis

Key comments received

- American College of Radiology (ACR)
 - Recommend BI-RADS Fifth Edition (December 2013)
 - The breasts are heterogeneously dense, which may obscure detection of small masses
 - The breasts are extremely dense, which lowers the sensitivity of mammography
 - HHUS: adverse impact on interpreting physician workforce
 - Evidence on HHUS: physician-performed; 19 minutes
 - Insufficient numbers of interpreting physicians in CA
 - Consider separating heterogeneously from extremely dense

Key comments received #2

- Judy Dean, MD; Co-author Kelly 2010; Shareholder
 - Assumption that ABUS = HHUS is wrong
 - Kelly 2010: PPV3 30.7% to 38.4%
- Hologic
 - Use of DBT as first-line screen rather than after DM
 - Efficient, reduces false positives
 - 2D reconstruction algorithms FDA approved May 2013
 - No increase in radiation over DM



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Model of Clinical and Economic Outcomes of Supplemental Screening in Women with Dense Breast Tissue

Janie M. Lee, MD, MSc
Seattle Cancer Care Alliance
University of Washington

September 25, 2013

Model Overview

- Population-based model of screening-eligible* California women, age 40-74, receiving:
 - Mammographic screening (in all women, DM vs FM)
 - Supplemental screening (BI-RADS 3 or 4 density and negative mammogram):
 - 45% of all CA women with negative mammograms: ~2.8 million
 - Heterogeneously dense: ~2.3 million; Extremely dense: ~500,000
- Supplemental modalities: HHUS/ABUS, MRI, DBT†

*Excludes: personal hx of breast cancer, hx of mantle radiation to chest, presence of genetic risk factors

†HHUS: handheld ultrasound; ABUS: automated breast ultrasound; MRI: magnetic resonance imaging;

DBT: digital breast tomosynthesis

Model Overview

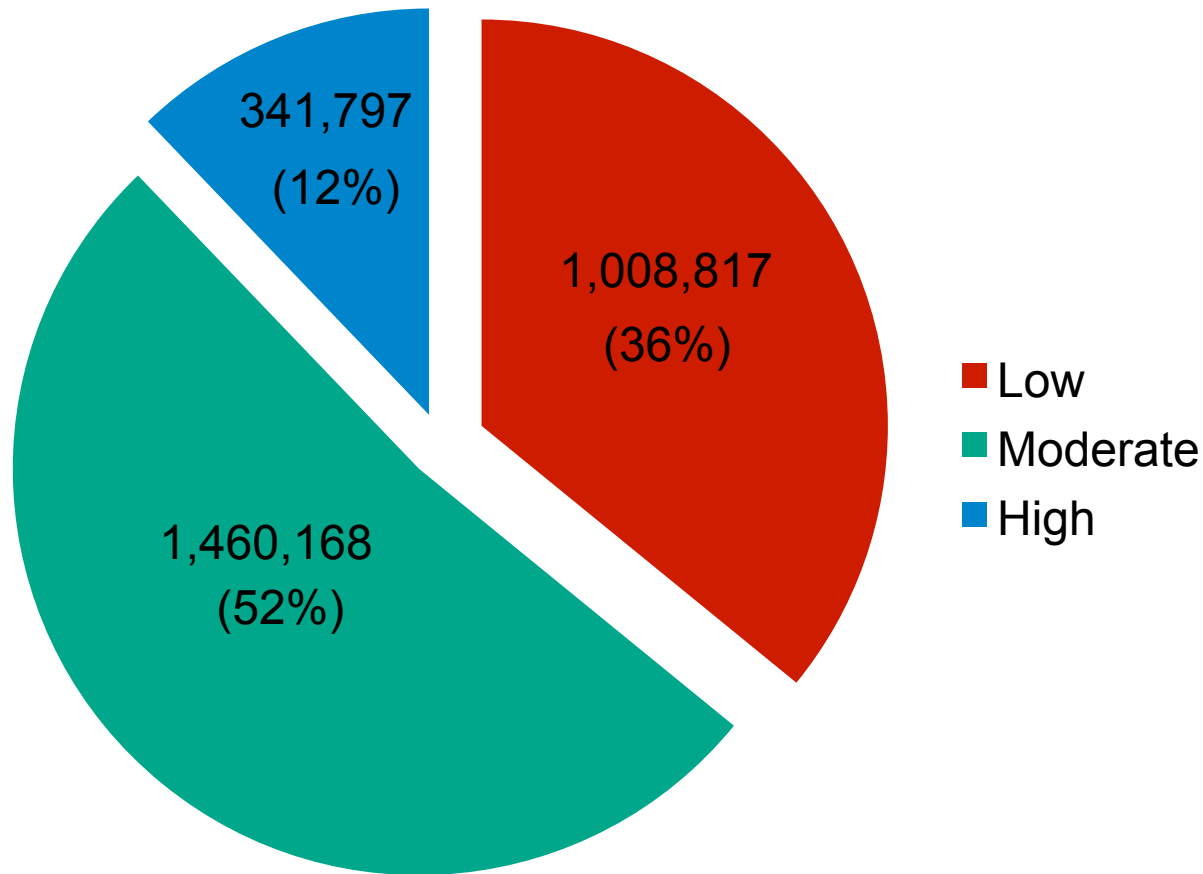
- Focus on 1-year “diagnostic pathway” for cancer detection:
 - Mammographic and supplemental screening
 - Additional diagnostic imaging - “Recalls”
 - Biopsy
- Outcomes of interest:
 - Recall/biopsy rates
 - Cancers detected
 - False positives
 - Interval cancers
- Cancer treatment *not* considered

Breast Cancer Risk

- Women entering the model were further placed into risk categories, based on:
 - Breast density, age, family history (1st degree relative)
- Calculated using 5-year risks for women with dense breasts from BCSC Risk Calculator*:
 - **Low** (age 40-49, no family hx): <1.7% (risk assumed in model: 1%)
 - **Moderate** (age 40-49 w/family hx OR age 50+, no family hx): 1.7-3.0% (risk assumed in model: 2.5%)
 - **High** (age 50+ w/family hx): >3.0% (risk assumed in model: 5.0%)

*Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Annals of internal medicine*. Mar 4 2008;148(5):337-347.

Breast Cancer Risk: California Women w/Dense Breast Tissue & Negative DM



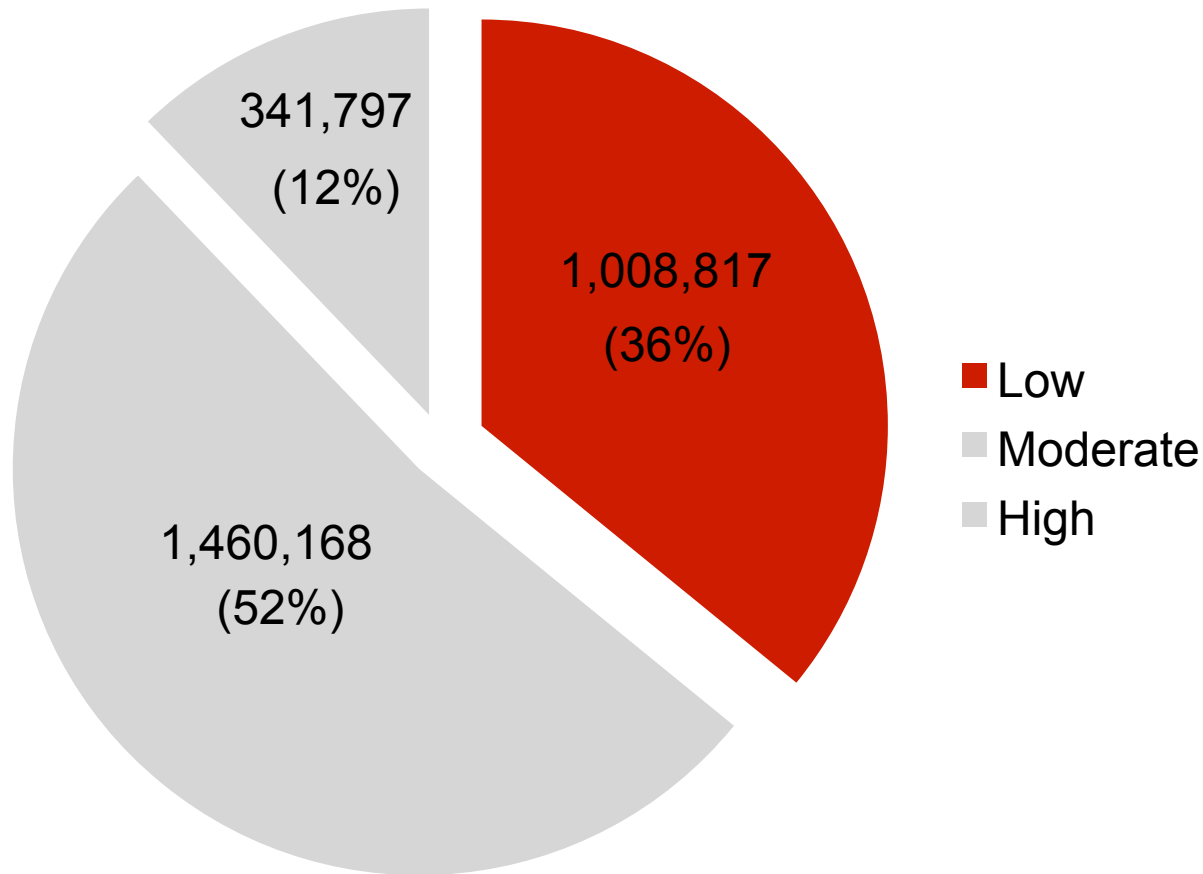
Key Assumptions

- Perfect compliance with mammographic and supplemental screening
- All positive supplemental screening tests result in biopsy
- Supplemental tests detect:
 - Percentage of cancers that would become interval cancers
 - Additional cancers not identified by screening mammography
- HHUS and ABUS have equivalent clinical performance
- Supplemental screening with DBT would include repeat DM
- Between 10% and 30% of additional cancers detected by supplemental screening may be “overdiagnosis”

Costs

- Digital mammographic screening
 - Medicare Fee Schedule
- Supplemental screening
 - MRI & HHUS: Medicare Fee Schedule
 - ABUS: HHUS + add'l code for 3D views
 - DBT: DM + \$50 “patient contribution”
- Additional diagnostic imaging / Biopsy
 - Recalls following screening mammography
 - Biopsy costs after positive supplemental screening
 - Women with interval cancers presenting clinically

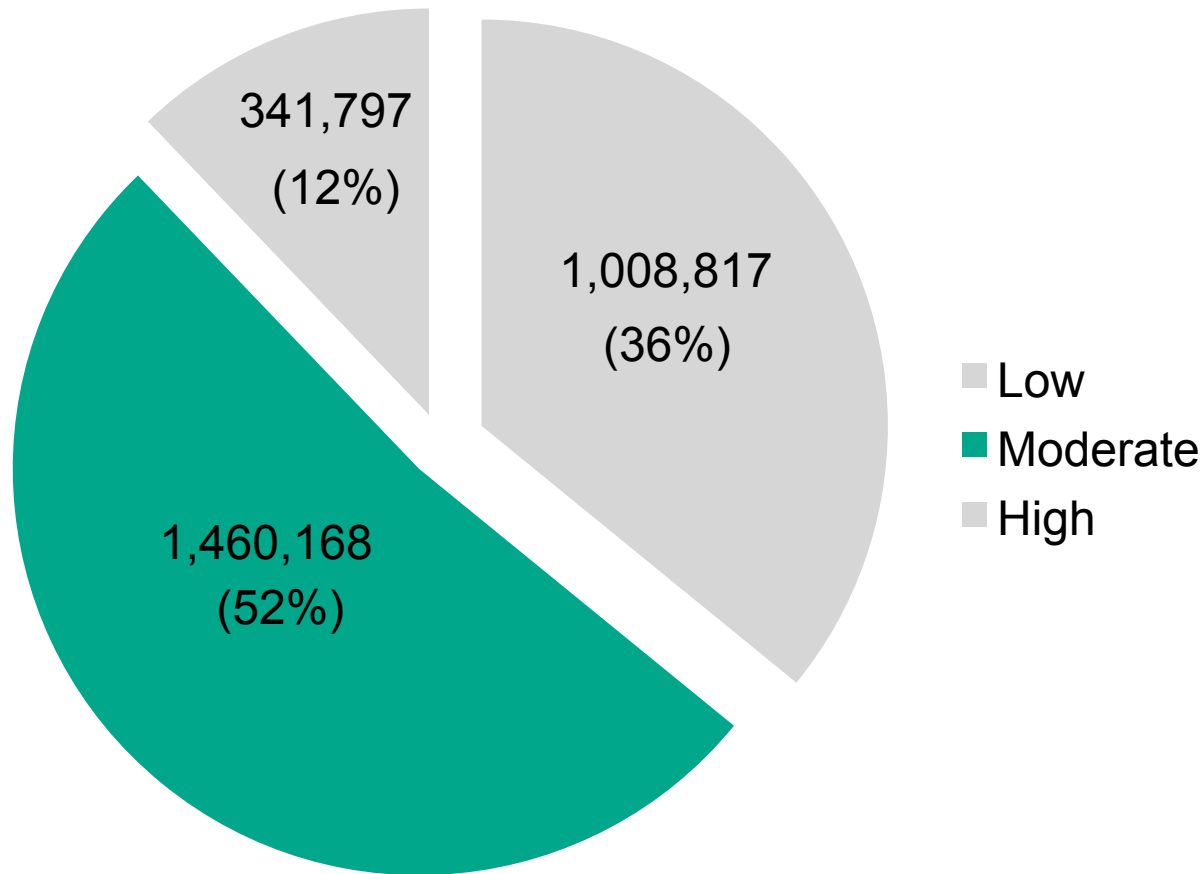
Impact of Supplemental Screening: Women at Low Breast Cancer Risk



Results: Incremental Effects of Supplemental Screening (Low Risk)

| Outcome (per 1,000 screened) | DM Alone | DM+MRI | DM+HHUS/ ABUS | DM+DBT |
|-----------------------------------|----------|--------|------------------|--------|
| Cancers Detected (True Positives) | 1.6 | +3.4 | +1.8 | +1.5 |
| False Positive Biopsy | 4.6 | +19.1 | +23.3 | +6.2 |
| Cancers Missed (Interval Cancers) | 0.4 | (0.3) | (0.3) | (0.3) |
| Cost (per Woman Screened, \$) | 185 | +657 | +124/+206 | +206 |

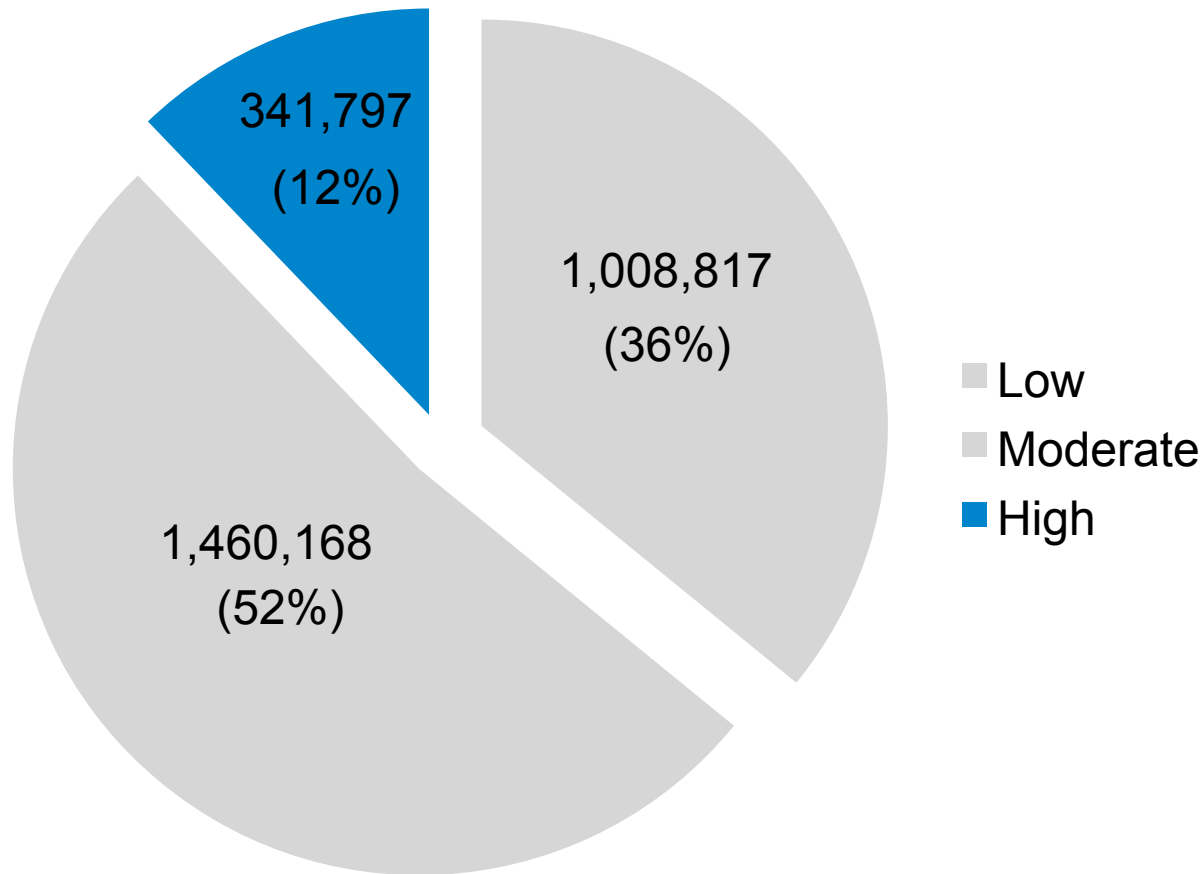
Impact of Supplemental Screening: Women at Moderate Breast Cancer Risk



Results: Incremental Effects of Supplemental Screening (Moderate Risk)

| Outcome (per 1,000 screened) | DM Alone | DM+MRI | DM+HHUS/ ABUS | DM+DBT |
|-----------------------------------|----------|--------|------------------|--------|
| Cancers Detected (True Positives) | 3.9 | +6.5 | +4.4 | +4.1 |
| False Positive Biopsy | 11.6 | +26.1 | +46.9 | +12.2 |
| Cancers Missed (Interval Cancers) | 1.1 | (1.0) | (0.9) | (0.8) |
| Cost (per Woman Screened, \$) | 193 | +666 | +148/+231 | +214 |

Impact of Supplemental Screening: Women at High Breast Cancer Risk

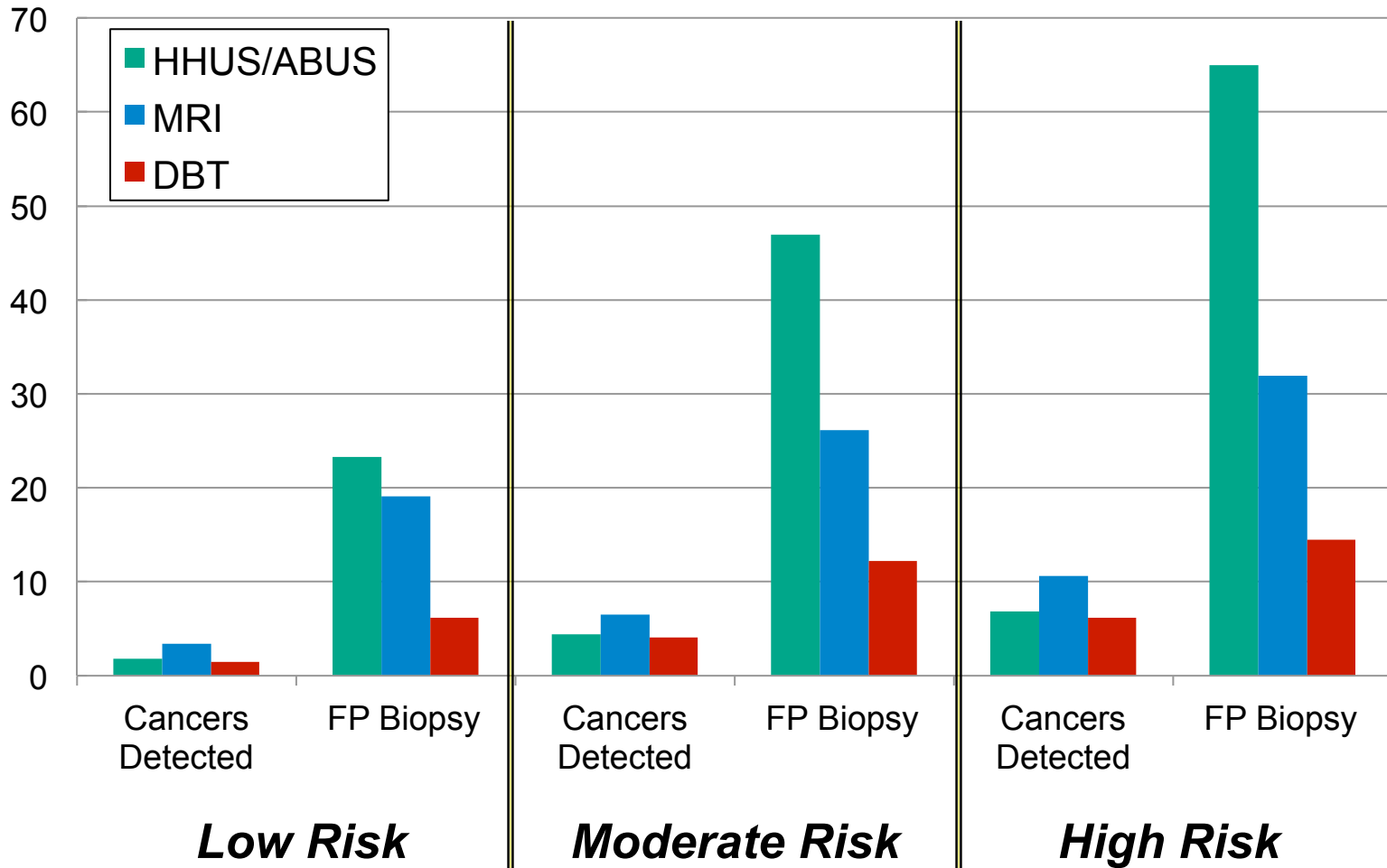


Results: Incremental Effects of Supplemental Screening (High Risk)

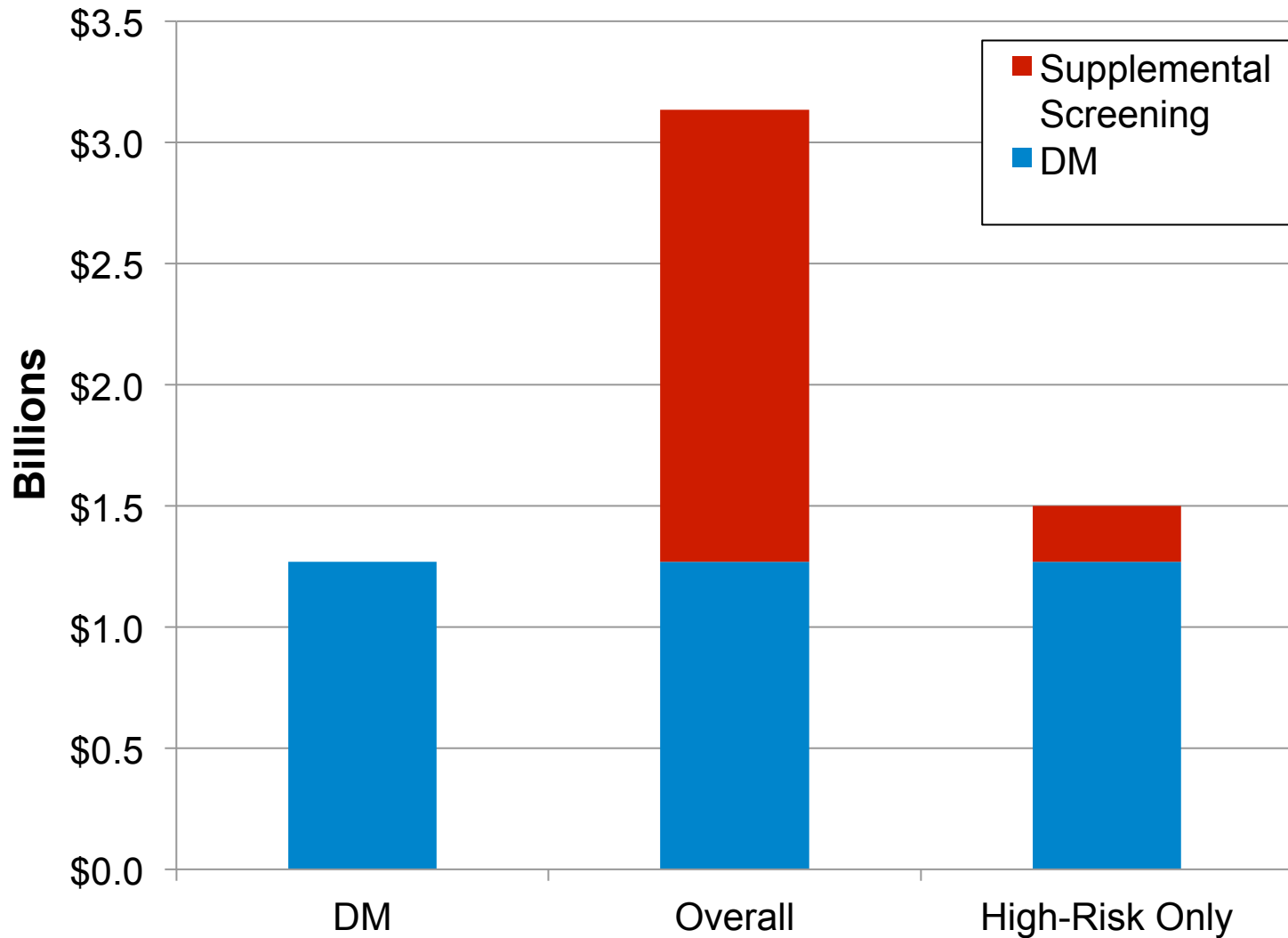
| Outcome (per 1,000 screened) | DM Alone | DM+MRI | DM+HHUS/ ABUS | DM+DBT |
|-----------------------------------|----------|--------|------------------|--------|
| Cancers Detected (True Positives) | 7.9 | +10.6 | +6.8 | +6.2 |
| False Positive Biopsy | 23.2 | +31.9 | +65.0 | +14.5 |
| Cancers Missed (Interval Cancers) | 2.1 | (2.1) | (1.8) | (1.7) |
| Cost (per Woman Screened, \$) | 199 | +676 | +167/+250 | +219 |

Incremental Effects, by Breast Cancer Risk

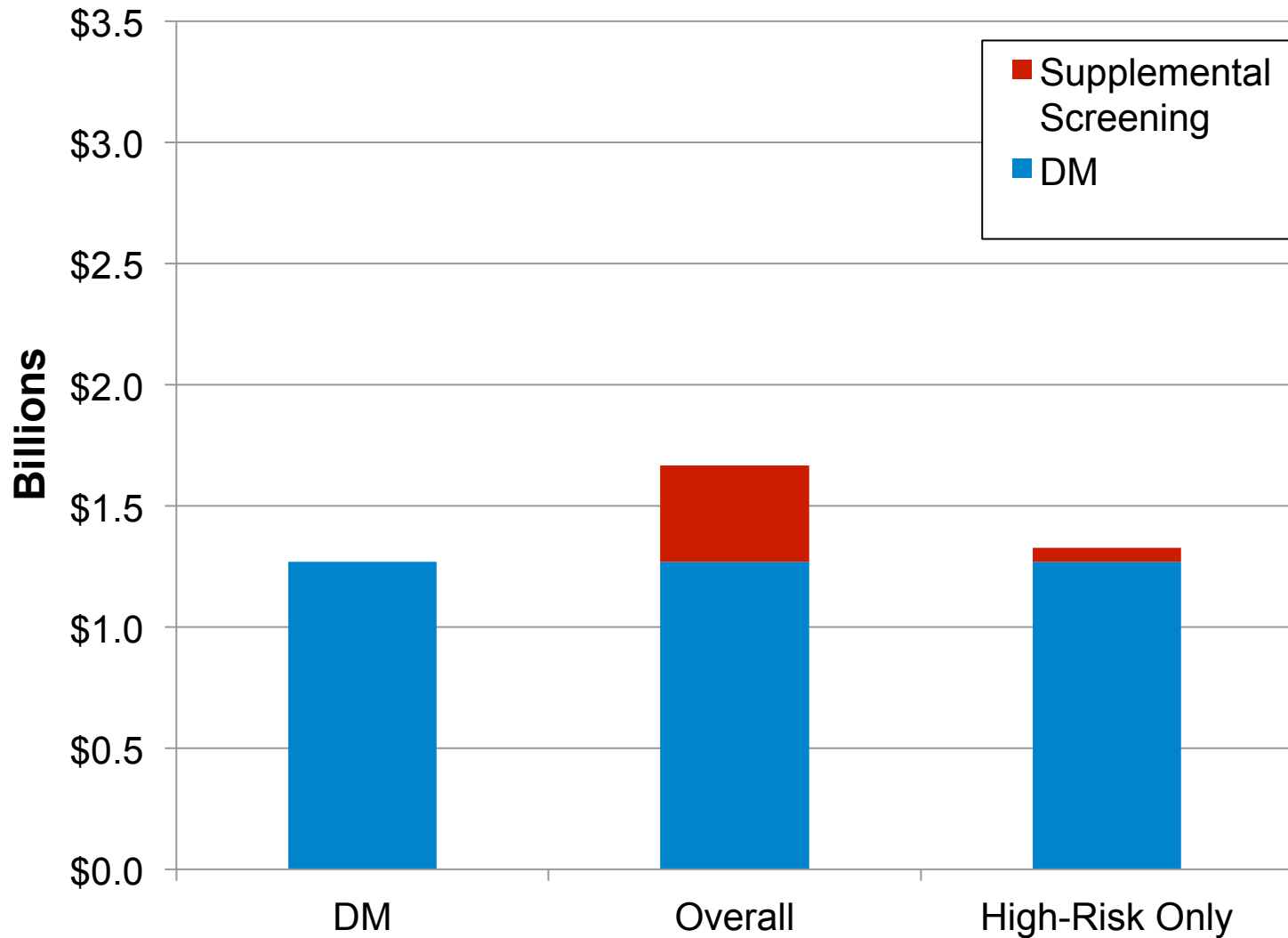
Outcome (per 1,000 screened)



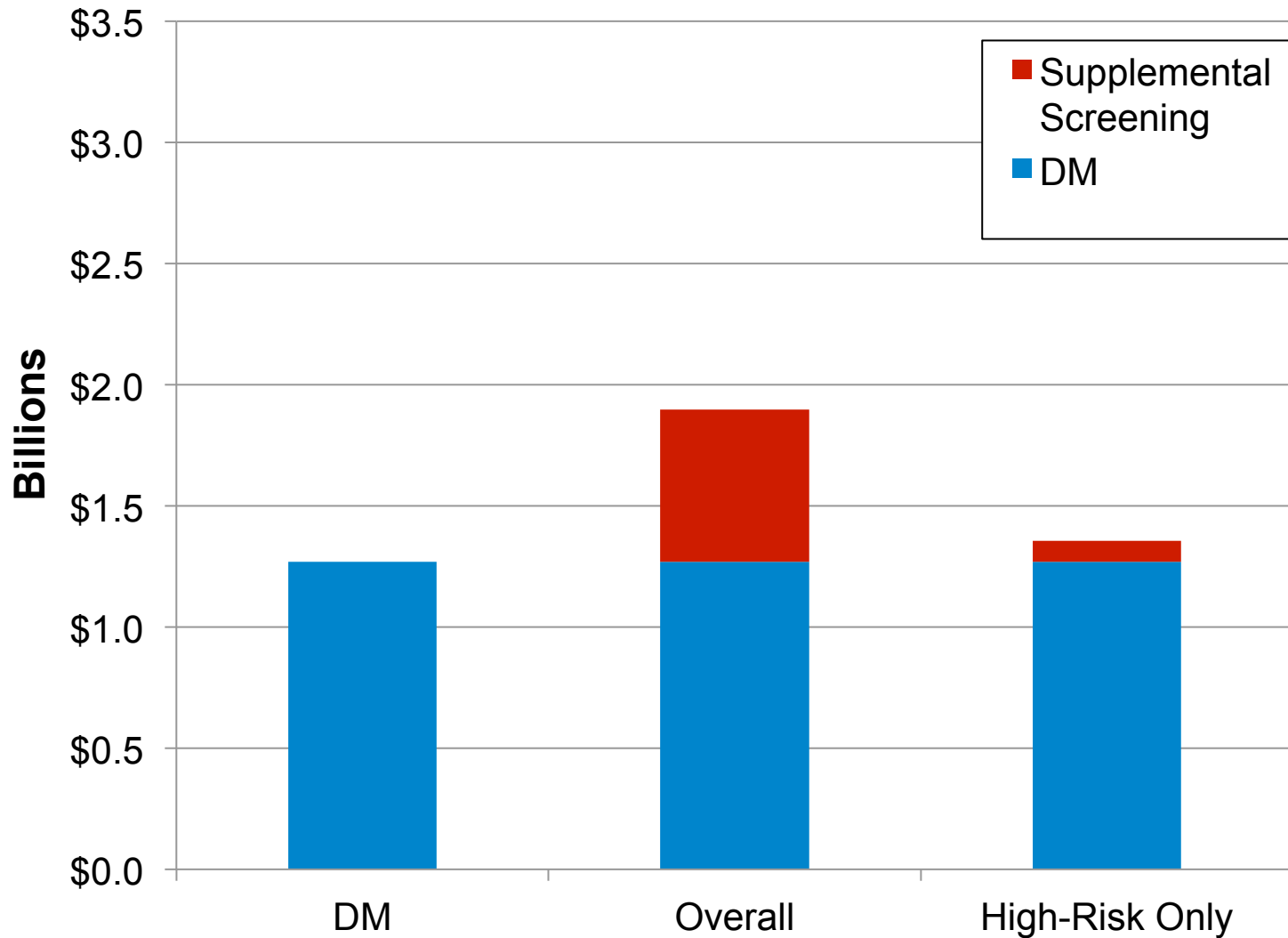
Budget Impact of Supplemental Screening with MRI



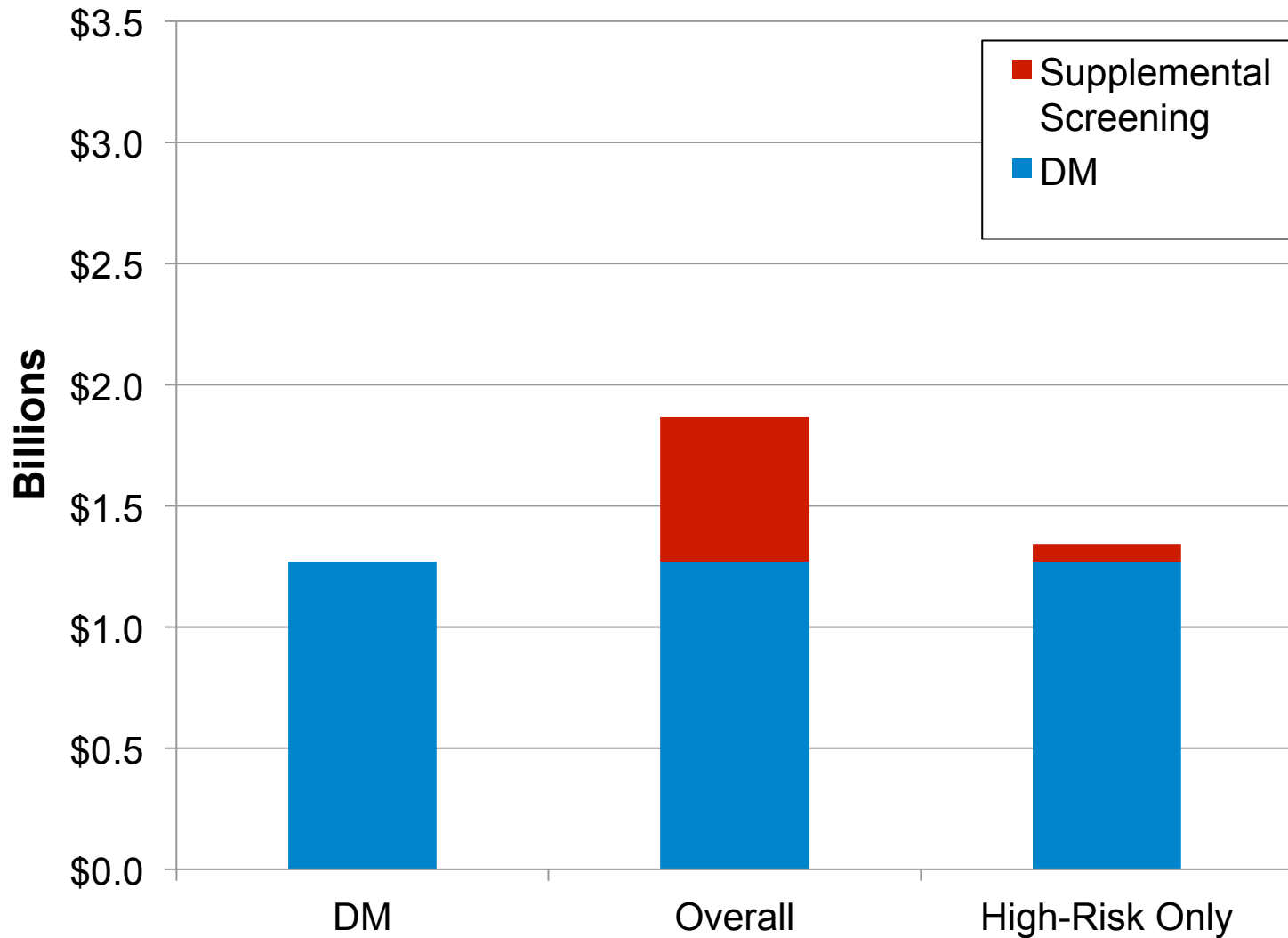
Budget Impact of Supplemental Screening with HHUS



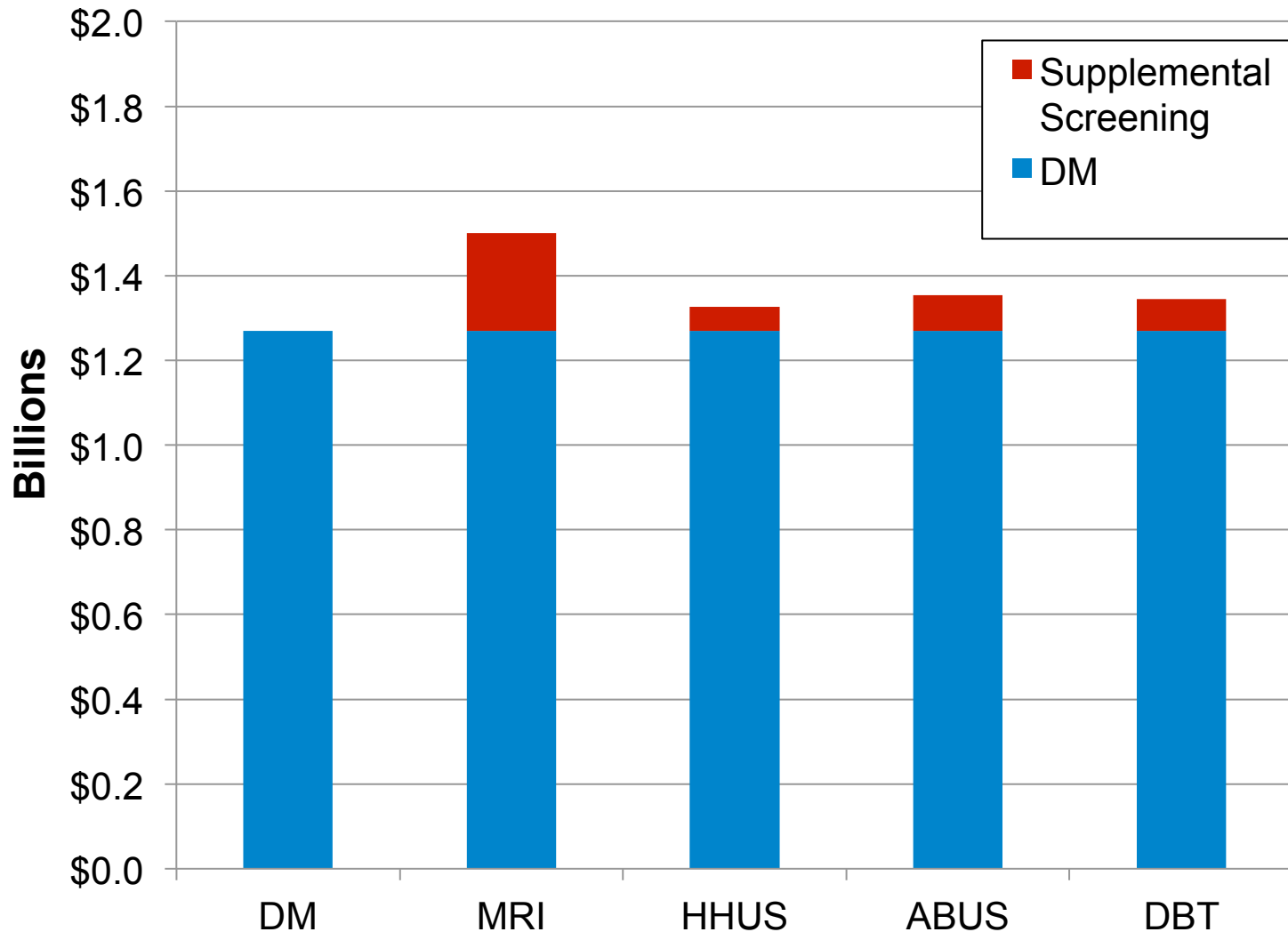
Budget Impact of Supplemental Screening with ABUS



Budget Impact of Supplemental Screening with DBT



Budget Impact of Supplemental Screening, All Modalities (High Risk Only)



Model Limitations

- Assumption of perfect compliance with mammographic and supplemental screening → likely overestimates of cancer detection and cost
- Supplemental use of DBT vs. use as replacement for DM alone in all women → likely overestimate of cost
- Estimates of cancer detection for supplemental modalities extrapolated from different populations:
 - E.g., MRI studies in very high-risk women

Summary

- Clinical tradeoffs apparent with each supplemental modality:
 - MRI detects the greatest number of cancers, and is most expensive
 - HHUS/ABUS is lowest cost to implement, and generates the greatest number of false-positive biopsies
 - DBT has lowest FP biopsy rate, but evidence base does not involve use as a supplemental screening test
- Greatest cancer yield and smallest budget impact projected with most selective application of supplemental screening
 - Women ages 50+ and close family history

Thank you!

Additional slides

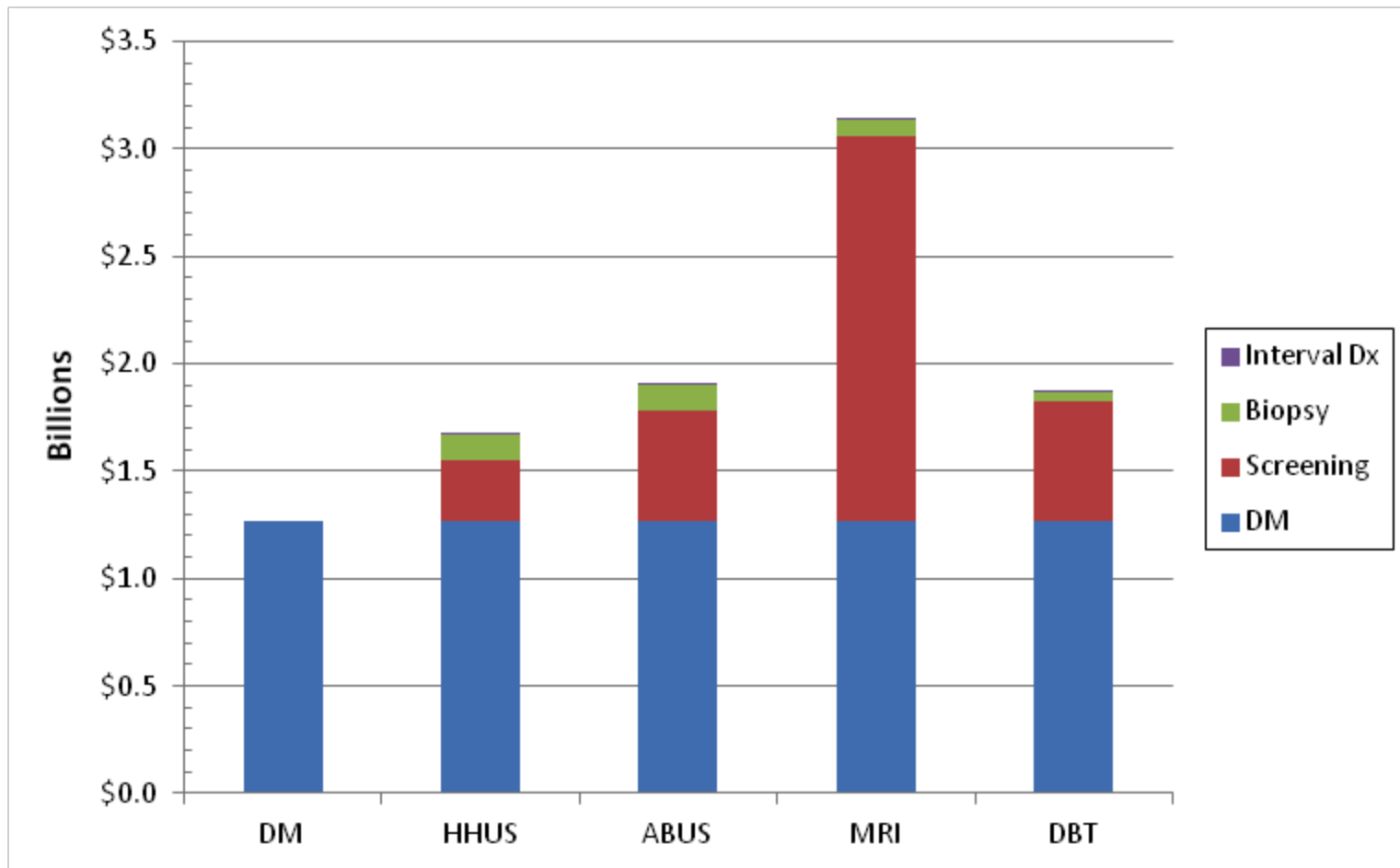
Results: Digital vs. Film Mammography (Dense Breasts)

| Outcome (per 1,000 screened) | Film | Digital |
|-----------------------------------|-------|---------|
| Recalls | 120.0 | 128.0 |
| Biopsies Performed | 16.2 | 17.8 |
| Cancers Detected (True Positives) | 3.9 | 4.2 |
| False Positive (with Biopsy) | 12.3 | 13.6 |
| False Positive (without Biopsy) | 103.8 | 110.2 |
| Cancers Missed (Interval Cancers) | 1.1 | 0.9 |
| Cost (per Woman Screened, \$) | 126 | 191 |

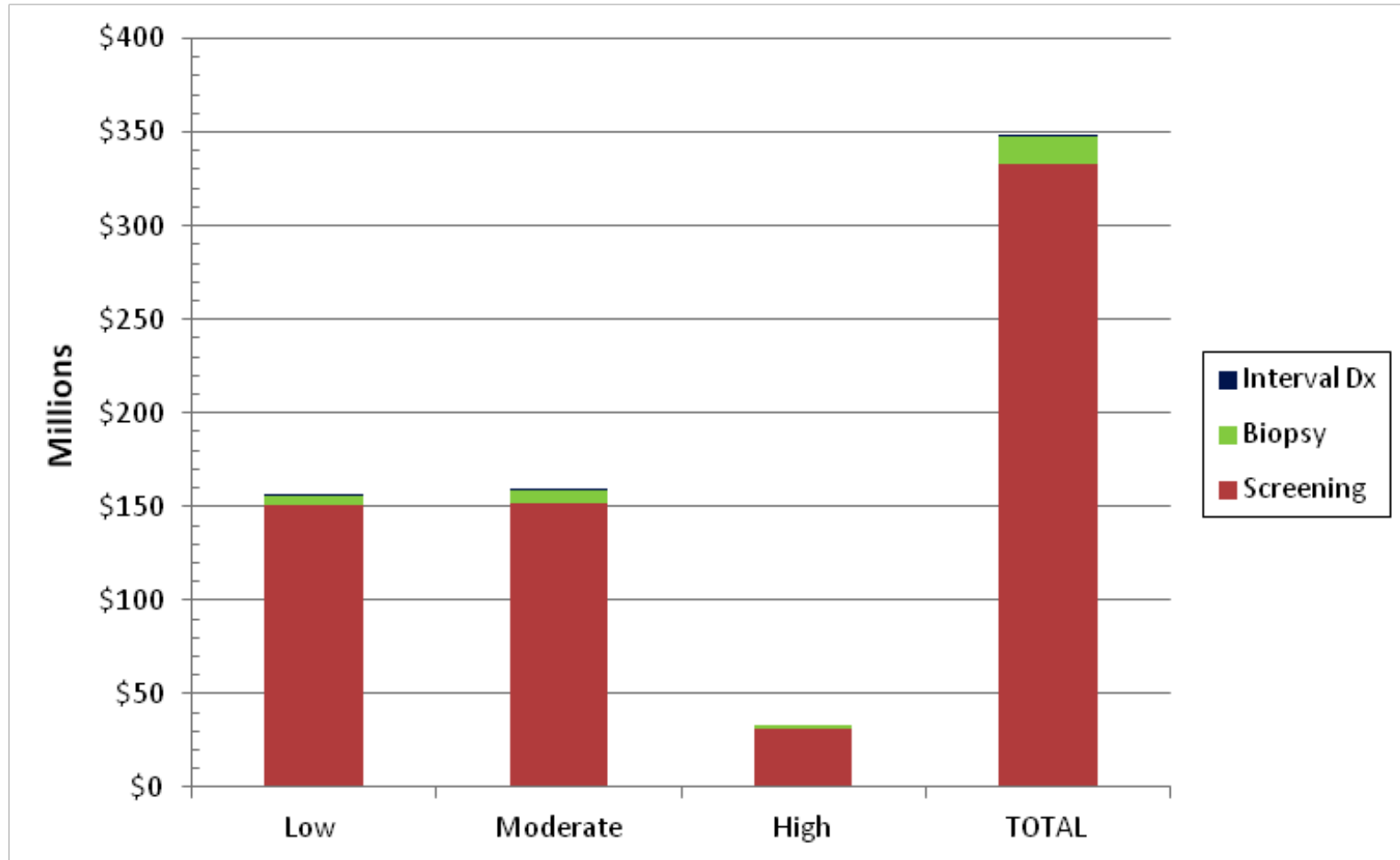
Results: Supplemental Screening (Overall Population)

| Outcome (per 1,000 screened) | DM+HHUS /ABUS | DM+MRI | DM+DBT | DM Alone |
|-----------------------------------|---------------|--------|--------|----------|
| Biopsies Performed | 62.2 | 48.0 | 31.5 | 17.8 |
| Cancers Detected (True Positives) | 8.0 | 10.1 | 7.6 | 4.2 |
| False Positive Biopsy | 54.2 | 37.9 | 23.9 | 13.6 |
| Cancers Missed (Interval Cancers) | 0.2 | 0.1 | 0.2 | 0.9 |
| Cost (per Woman Screened, \$) | 333/415 | 855 | 403 | 191 |

Overall Budget Impact to California (DM+Supplemental)



Impact of MRI Supplemental Screening (Extremely Dense Only)



Cost per Additional Case of Cancer Detected

| Risk | HHUS | ABUS | MRI | DBT |
|----------|----------|-----------|-----------|-----------|
| Low | \$67,916 | \$113,320 | \$194,713 | \$134,039 |
| Moderate | \$33,957 | \$52,937 | \$102,259 | \$52,874 |
| High | \$24,488 | \$36,613 | \$63,489 | \$35,189 |
| Overall | \$37,786 | \$59,860 | \$112,753 | \$62,095 |

Cost-Effectiveness Benchmarks

| Modality | Population | Result | Reference |
|---------------------------------------|---------------------------------|--|-------------------------------------|
| MRI+Mammography vs. Mammography Alone | Women 25-70 with BRCA mutations | \$124,000 per add'l breast cancer detected | Saadatmand et al., JNCI August 2013 |
| | | | |
| | | | |
| | | | |

Stakeholder Roundtable

Panelists

- **Sylvia Carlisle, MD – Anthem Wellpoint**
- **Christine Castano, MD – Health Care Partners**
- **Debbie Drake Dunne– Patient Advocate**
- **Meg Durbin, MD – Palo Alto Medical Foundation**
- **Laura Esserman, MD – UCSF**
- **Bonnie Joe, MD, PhD – UCSF**
- **Susan Kutner, MD – Kaiser Permanente, Northern California**
- **Joanne Schottinger, MD – Kaiser Permanente, Southern California**
- **Robert Smith, PhD – American Cancer Society**
- **John Yao, MD – Blue Shield of California Health Plan**

Closing

- Further public comments accepted until: Oct. 3, 2013
- Dissemination plans
- Next meeting: March 2014
- Next topic: To be posted by December 2013