



Supplemental Screening for Women with Dense Breast Tissue

Public Meeting – December 13, 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 – 11:45am**
- **Q&A with Roundtable Stakeholders | 11:45am – 12:30pm**
- **Lunch | 12:30pm – 1:15pm**
- **CEPAC Deliberation and Votes on Evidence Questions | 1:15pm – 2pm**
- **Roundtable Discussion | 2pm – 3:50pm**
- **Summary and Closing Remarks | 3:50pm – 4pm**



New England CEPAC

- Funding:
 - NESCSO
 - Regional private payers
 - Regional provider groups
- Goal:
 - To improve the application of evidence to guide practice and policy in New England
- Structure:
 - Evidence review from UCSF faculty; supplemented + updated by ICER
 - Deliberation and voting by CEPAC: independent clinicians, scientific review experts, and public representatives from all six New England states



New England CEPAC, cont.

- CEPAC recommendations designed to support aligned efforts to improve the application of evidence to:
 - Practice
 - Patient/clinician education
 - Quality improvement efforts
 - Clinical guideline development
 - Policy
 - Coverage and reimbursement
 - Medical management policies
 - Benefit design





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

Jeffrey A. Tice, MD
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

December 13, 2013

Conn. Gen. Stat. § 38a-503 a-M effective October 1, 2009

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

“If your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities, you might benefit from supplementary screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician's office and you should contact your physician if you have any questions or concerns about this report.”

- Also requires insurance coverage for supplemental screening with ultrasound:
 - MRI considered, but coverage ultimately mandated only for women at very high breast cancer risk (per ACS guidelines)

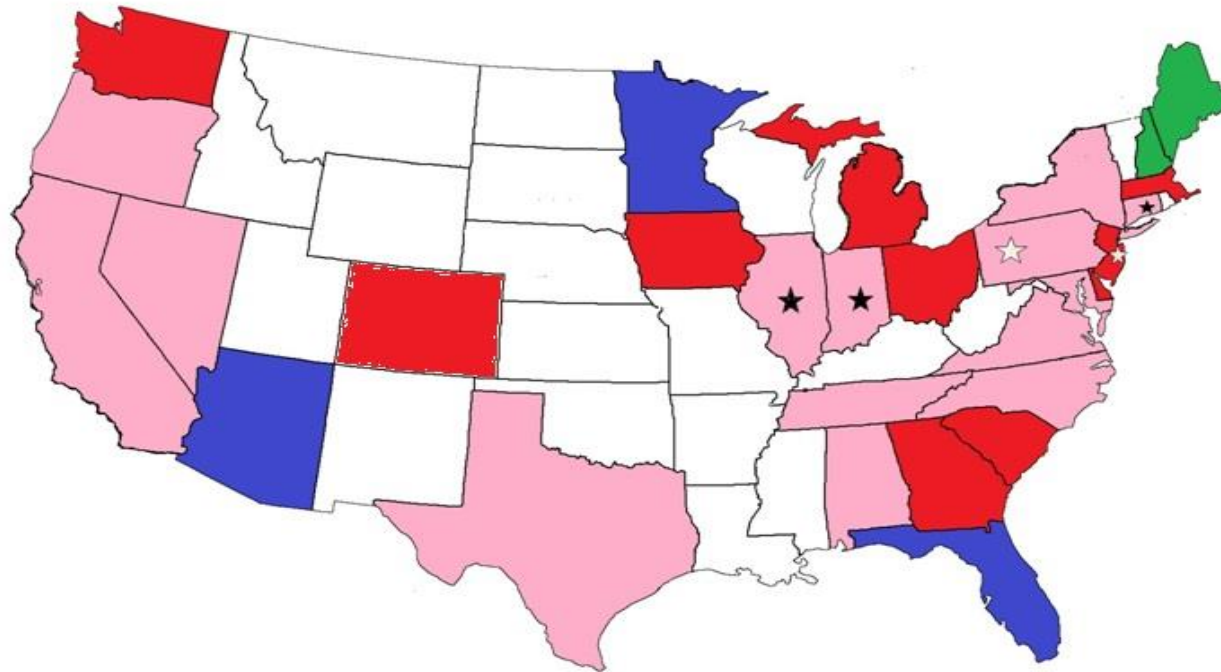


Legislative Status: Rest of New England

State	Status	Notification	Insurance Mandate
MA	Bill currently in committee	Yes	No
ME	Multi-stakeholder report recommending “lay letter”	Yes	No
NH	2012 notification bill deemed “inexpedient to legislate”	Yes	No
RI	No activity	---	---
VT	No activity	---	---

Are You DENSE?

exposing the best-kept secret®



- Pink = Law enacted
- Red = Law introduced
- Blue = Working on law
- Green = Law introduced, but no longer active
- ★ = Coverage mandated
- ☆ = Coverage mandate introduced



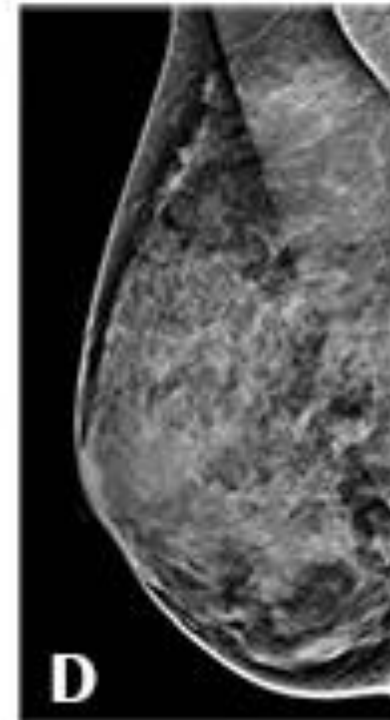
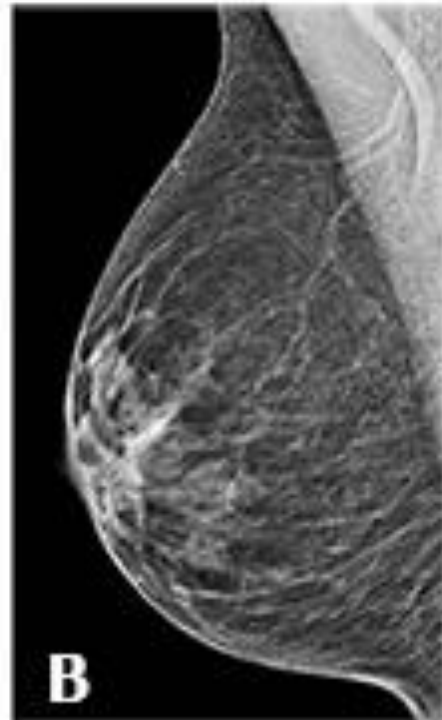
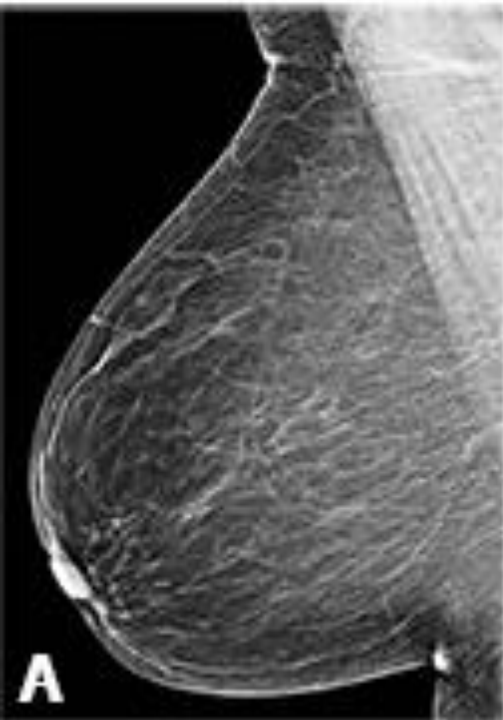
National Efforts

- Breast Density and Mammography Reporting Act:
 - First introduced in House of Representatives in 2011 (DeLauro/Israel)
 - Died in committee
 - Slated to be reintroduced late 2013; companion bill to be introduced in Senate (Feinstein)
- Mammography Quality Standards Act (MQSA):
 - FDA considering amendment to include breast density reporting



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
 - ~200,000 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	PPV %	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%



New Evidence

(Since Publication of Original Review)

- One single-center HHUS study identified*
- 800 women age 40-49 with dense breasts and negative mammogram
- Incremental CDR: 2.4 per 1000
- As with other studies, follow-up incomplete (interval cancer rates could not be calculated)
- Cost per add'l case of cancer detected: ~\$26,000

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

- BI-RADS Fifth Edition (January 2014)
 - New language for density and assessment
- 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
- Assessment biased
 - Against mammography, MRI, HHUS, ABUS, DBT
 - In favor of mammography, MRI, HHUS, ABUS, DBT
- New data are coming: don't rush to judgment



CLINICAL GUIDELINES/ COVERAGE POLICIES



Guidelines (ACS, NCCN, ACR)

- NCCN considers evidence insufficient to support routine supplemental screening in women w/dense breasts using any modality
- HHUS: Recommended by ACR
- ABUS: No recommendations
- MRI: Recommended by ACR, ACS, and NCCN only in women at very high breast cancer risk
- DBT: NCCN considers early evidence promising but insufficient to recommend for screening or diagnosis



Coverage Policies

- HHUS/ABUS: No regional public/private policies
 - Humana: no coverage for ABUS (investigational)
- MRI: Generally limited to women at very high breast cancer risk:
 - MassHealth: no coverage in asymptomatic, average-risk women
 - BCBSMA: considered investigational in women with dense breasts, breast implants, or scarring after treatment
- DBT: Generally not covered (investigational)
 - Connecticare: coverage w/prior authorization





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

**Daniel A. Ollendorf, ARM, MPH
Institute for Clinical and Economic Review**

December 13, 2013

Model Overview

- Population-based model of screening-eligible* New England women, age 40-74, receiving:
 - Mammographic screening (in all women, DM vs FM)
 - Supplemental screening (BI-RADS 3 or 4 density and negative mammogram):
 - 46% of all NE women with negative mammograms: ~1.4 million
 - Heterogeneously dense: ~1.2 million; Extremely dense: ~250,000
- 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

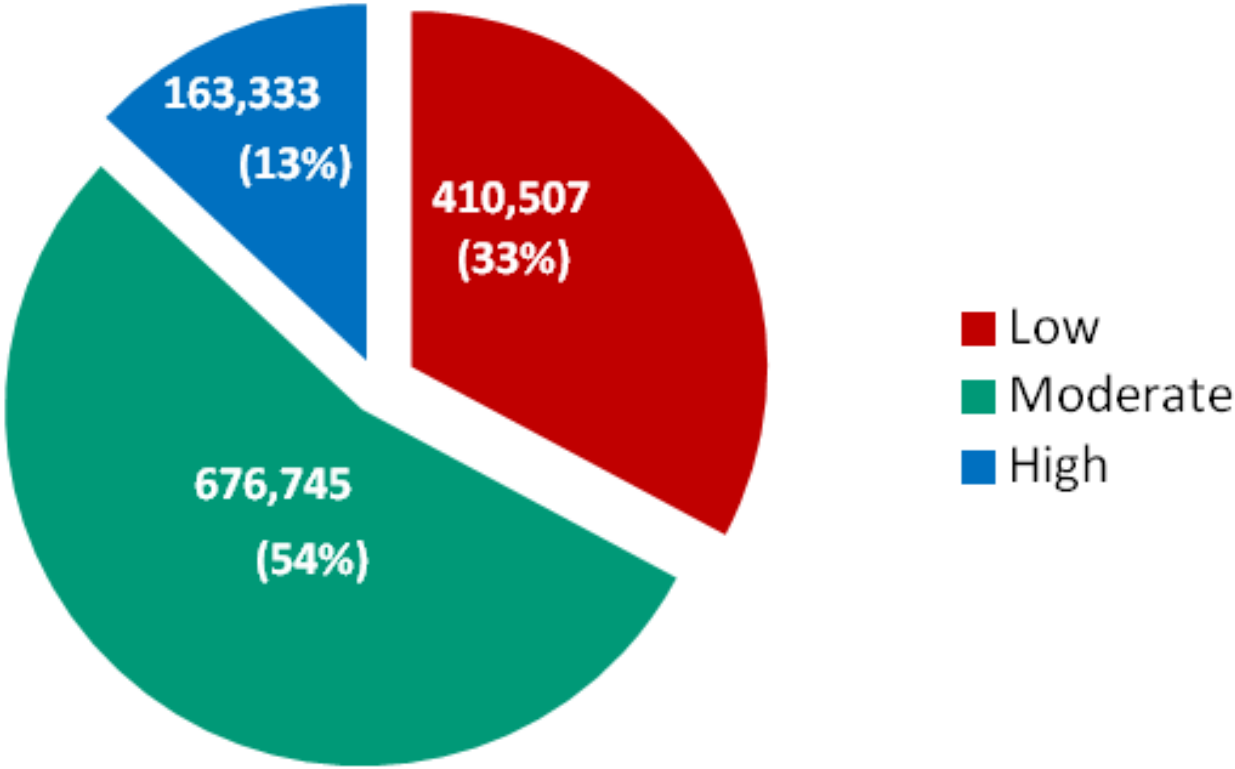
Breast Cancer Risk

- 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: New England Women w/Dense Breast Tissue & Negative DM



Key Assumptions

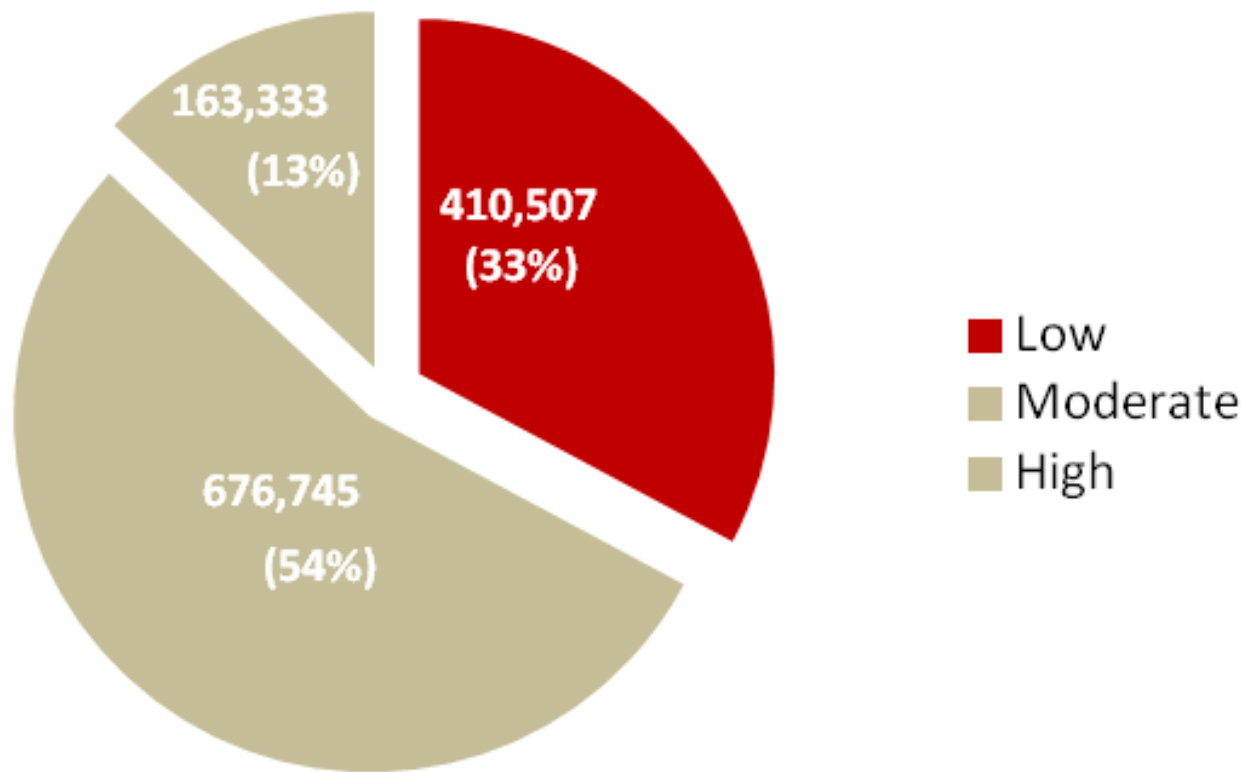
- Perfect compliance with mammographic and supplemental screening
- All positive supplemental screening tests result in biopsy
- Supplemental tests detect:
 - Percentage of cancers that would become interval cancers
 - Additional cancers not identified by screening mammography
- HHUS and ABUS have equivalent 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

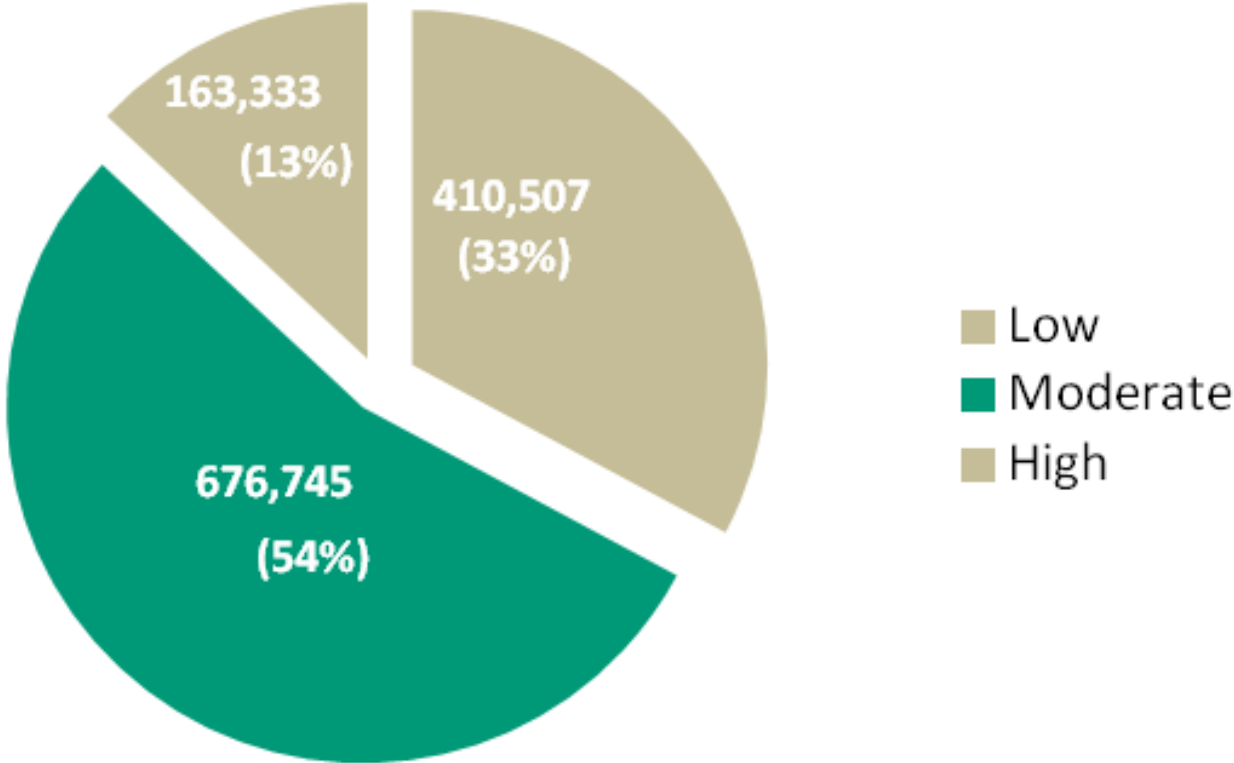
Impact of Supplemental Screening: Women at Low Breast Cancer Risk



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

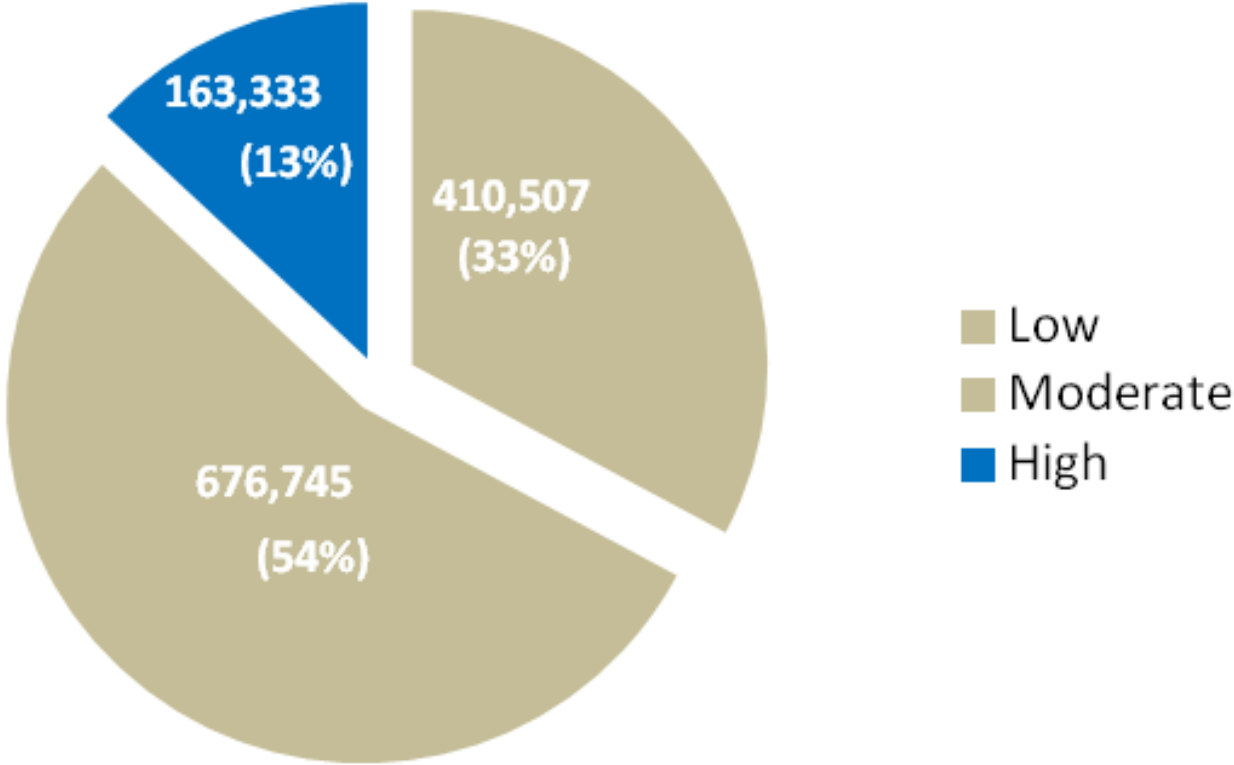
Impact of Supplemental Screening: Women at Moderate Breast Cancer Risk



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

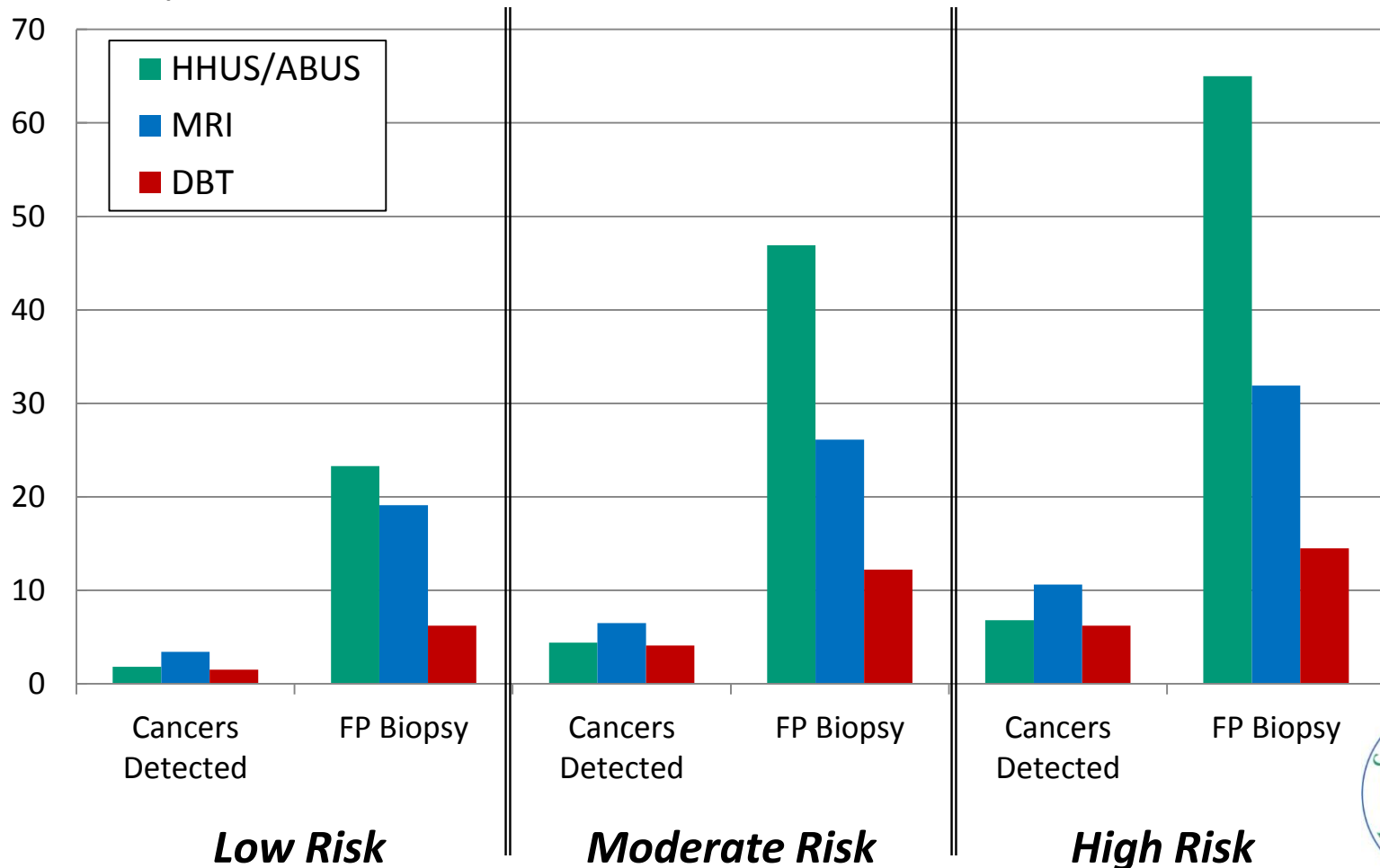


Results: Incremental Effects of Supplemental Screening (High Risk)

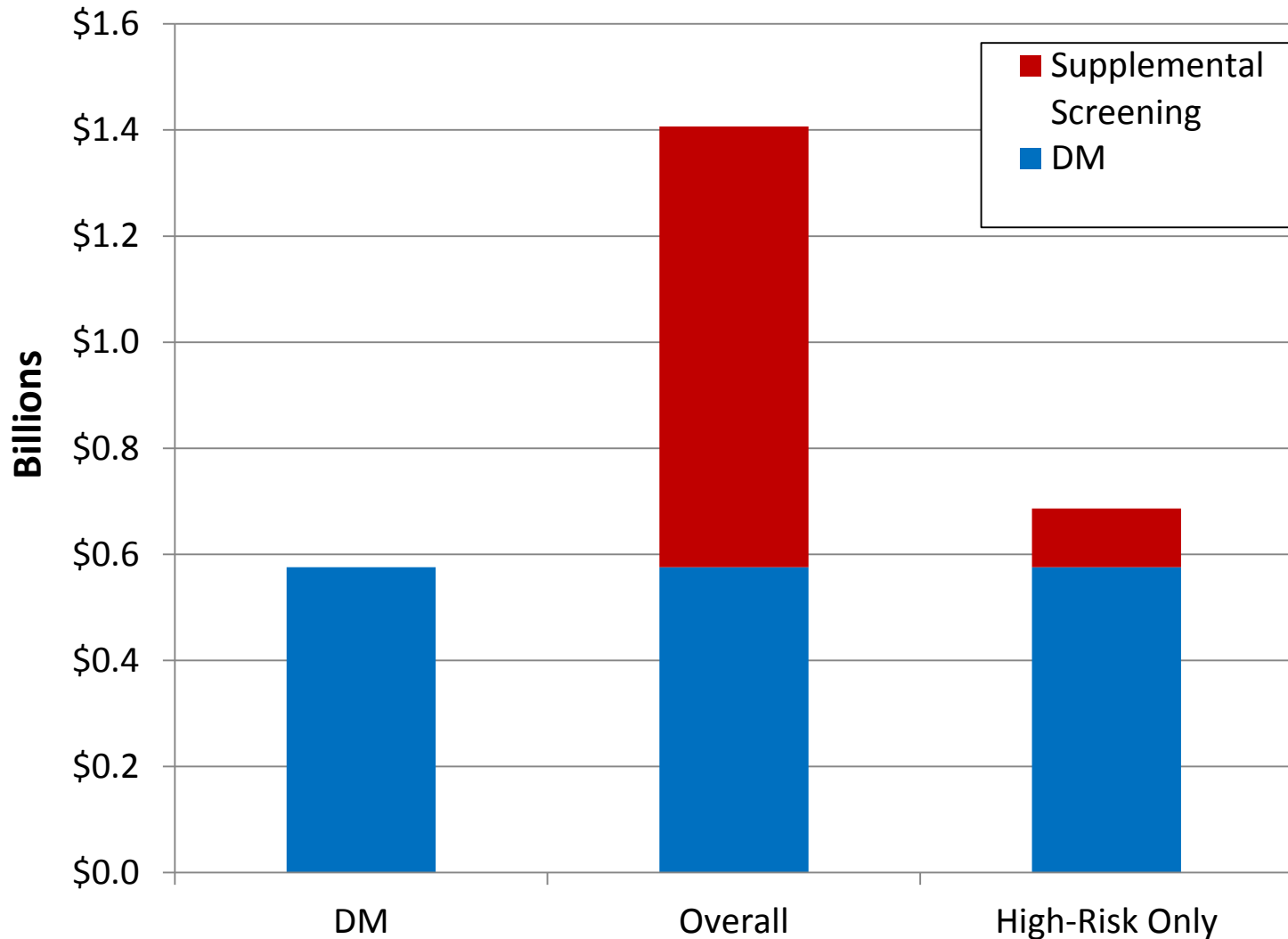
Outcome (per 1,000 screened)	DM Alone	DM+MRI	DM+HHUS/ ABUS	DM+DBT
Cancers Detected (True Positives)	7.9	+10.6	+6.8	+6.2
False Positive Biopsy	23.2	+31.9	+65.0	+14.5
Cancers Missed (Interval Cancers)	2.1	(2.1)	(1.8)	(1.7)
Cost (per Woman Screened, \$)	199	+676	+167/+250	+219

Incremental Effects, by Breast Cancer Risk

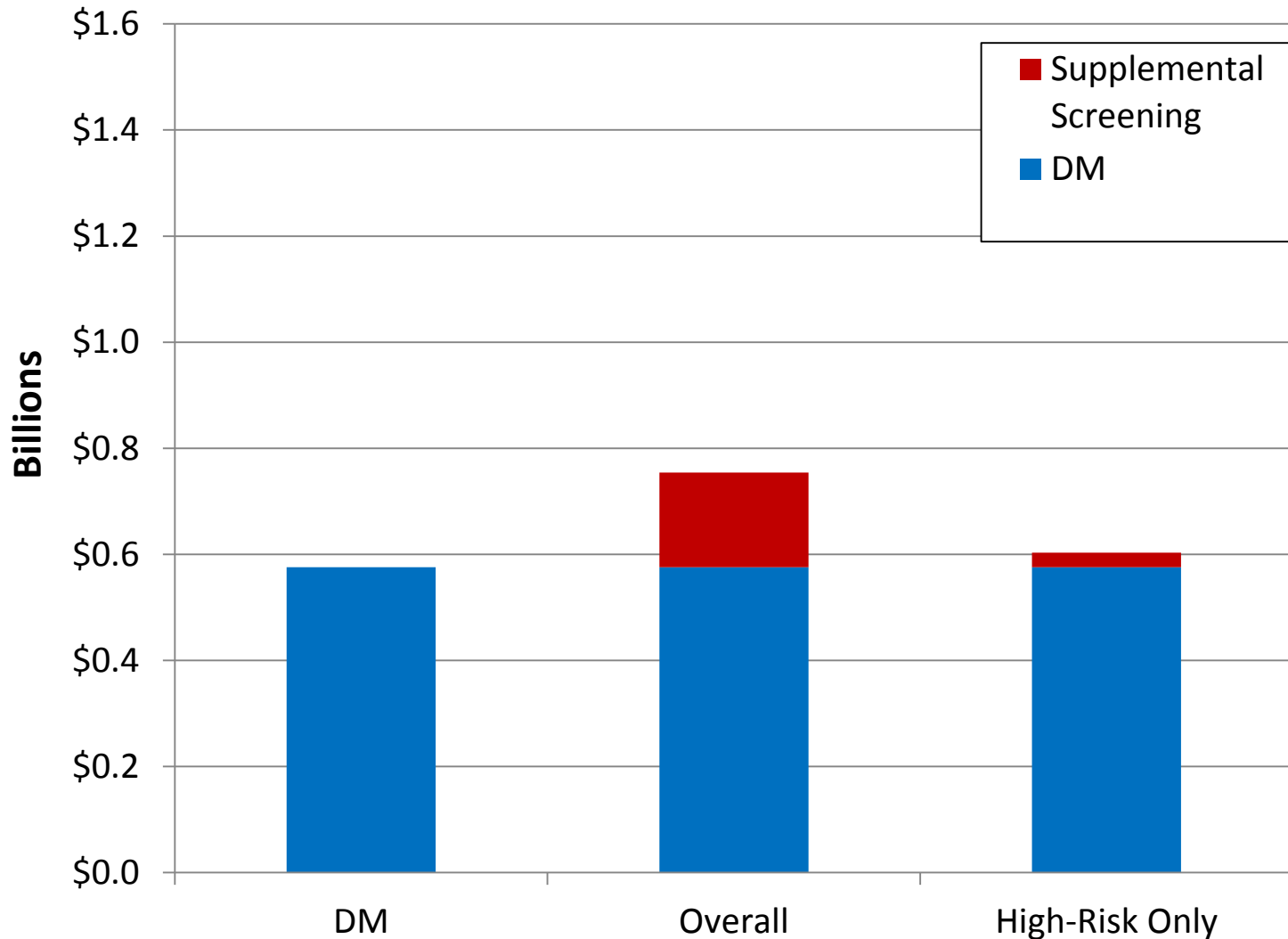
Outcome (per 1,000 screened)



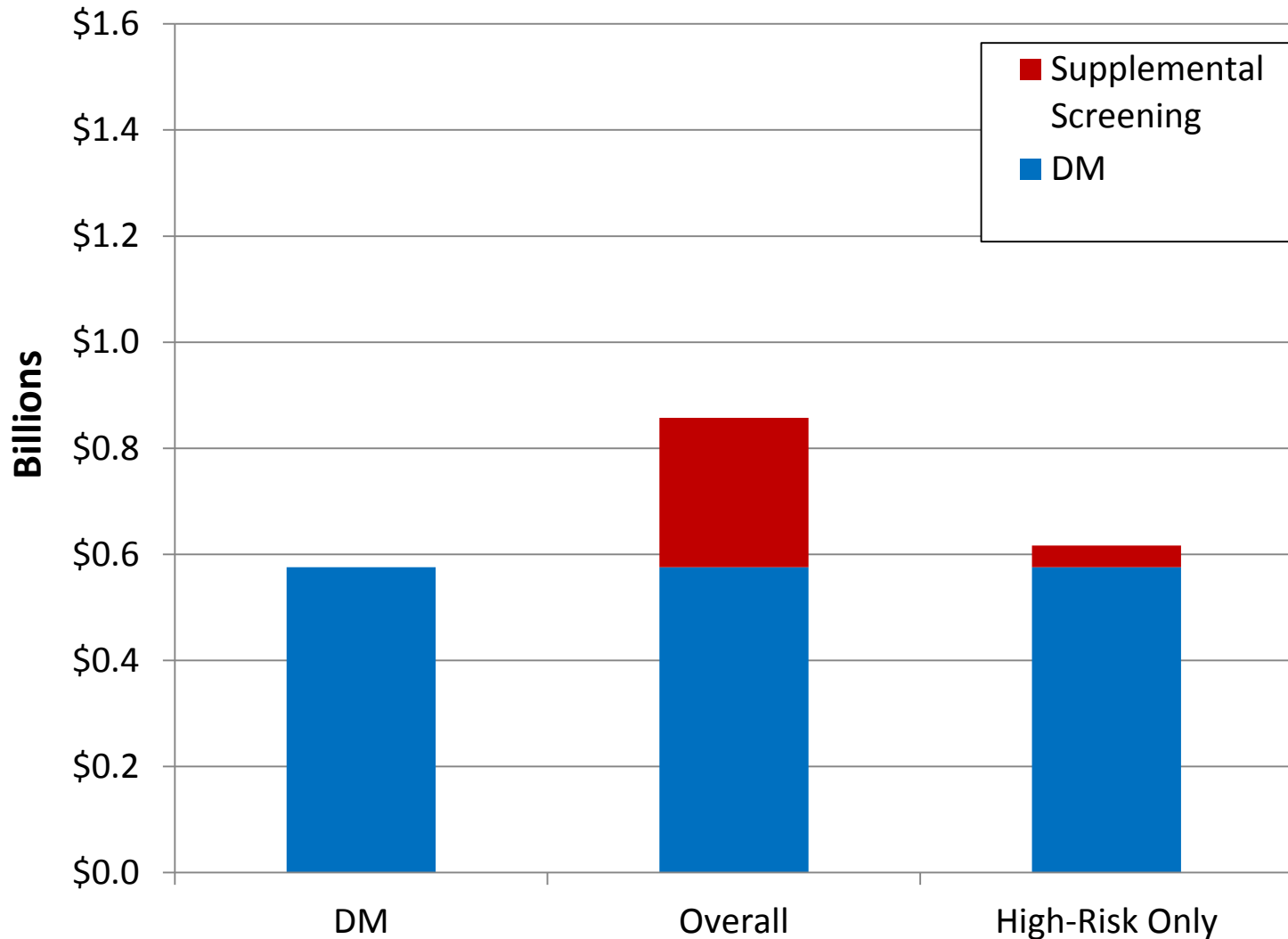
Budget Impact of Supplemental Screening with MRI



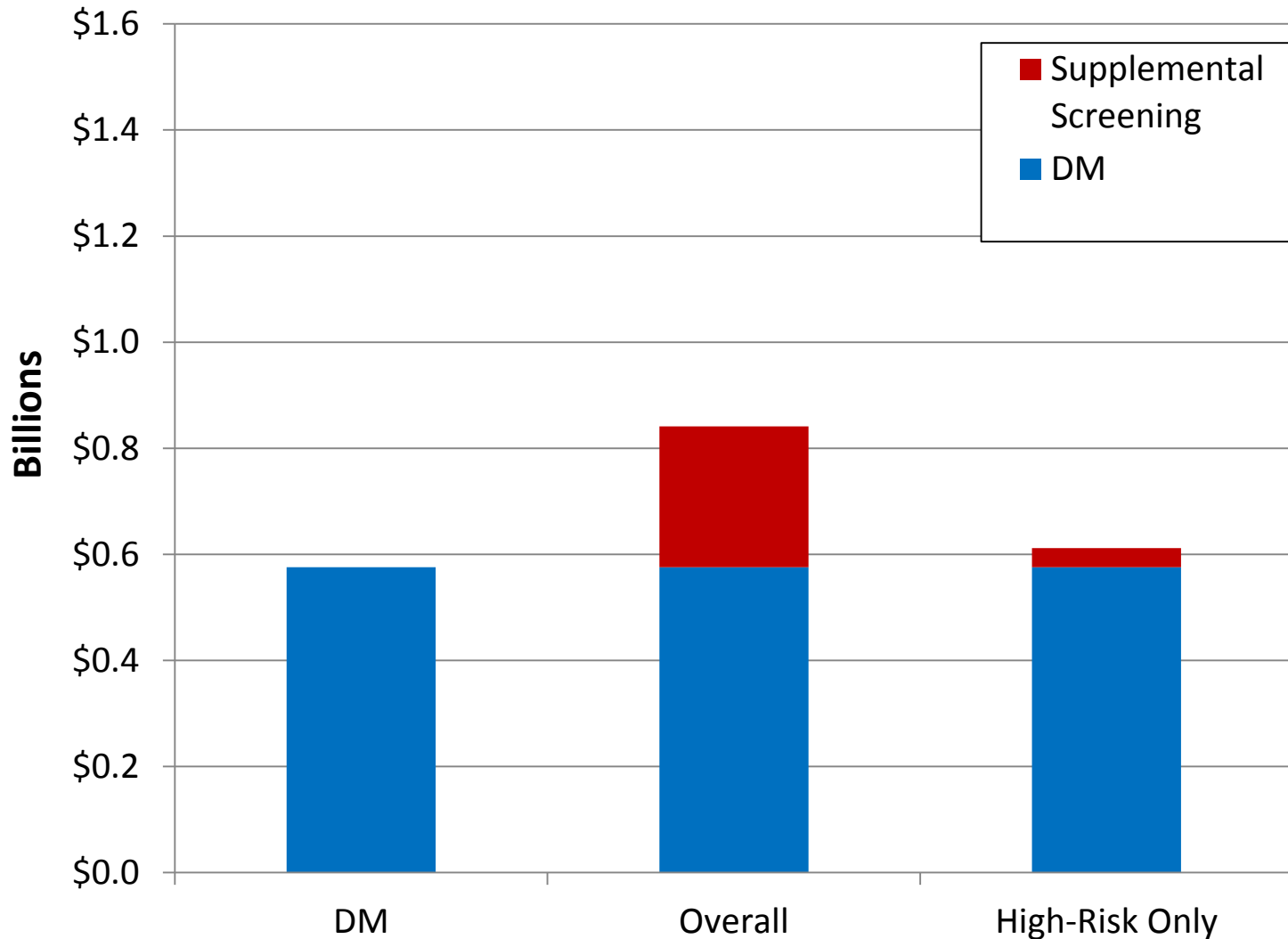
Budget Impact of Supplemental Screening with HHUS



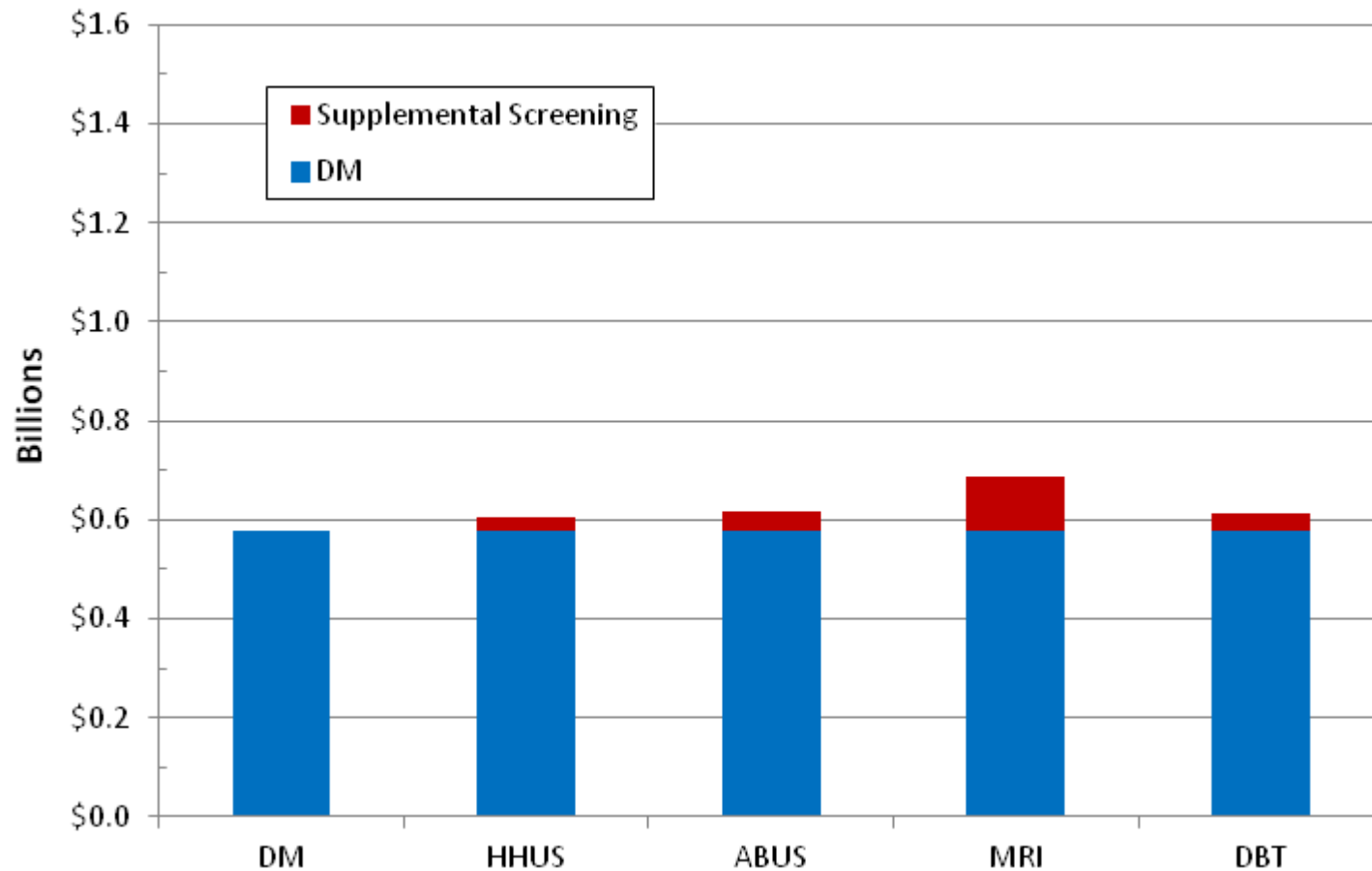
Budget Impact of Supplemental Screening with ABUS



Budget Impact of Supplemental Screening with DBT



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



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
HHUS+Mammography vs. Mammography Alone	Women 40-49 with dense breasts and negative mammogram	\$26,000 per add'l breast cancer detected	Venturini et al., Radiology August 2013

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

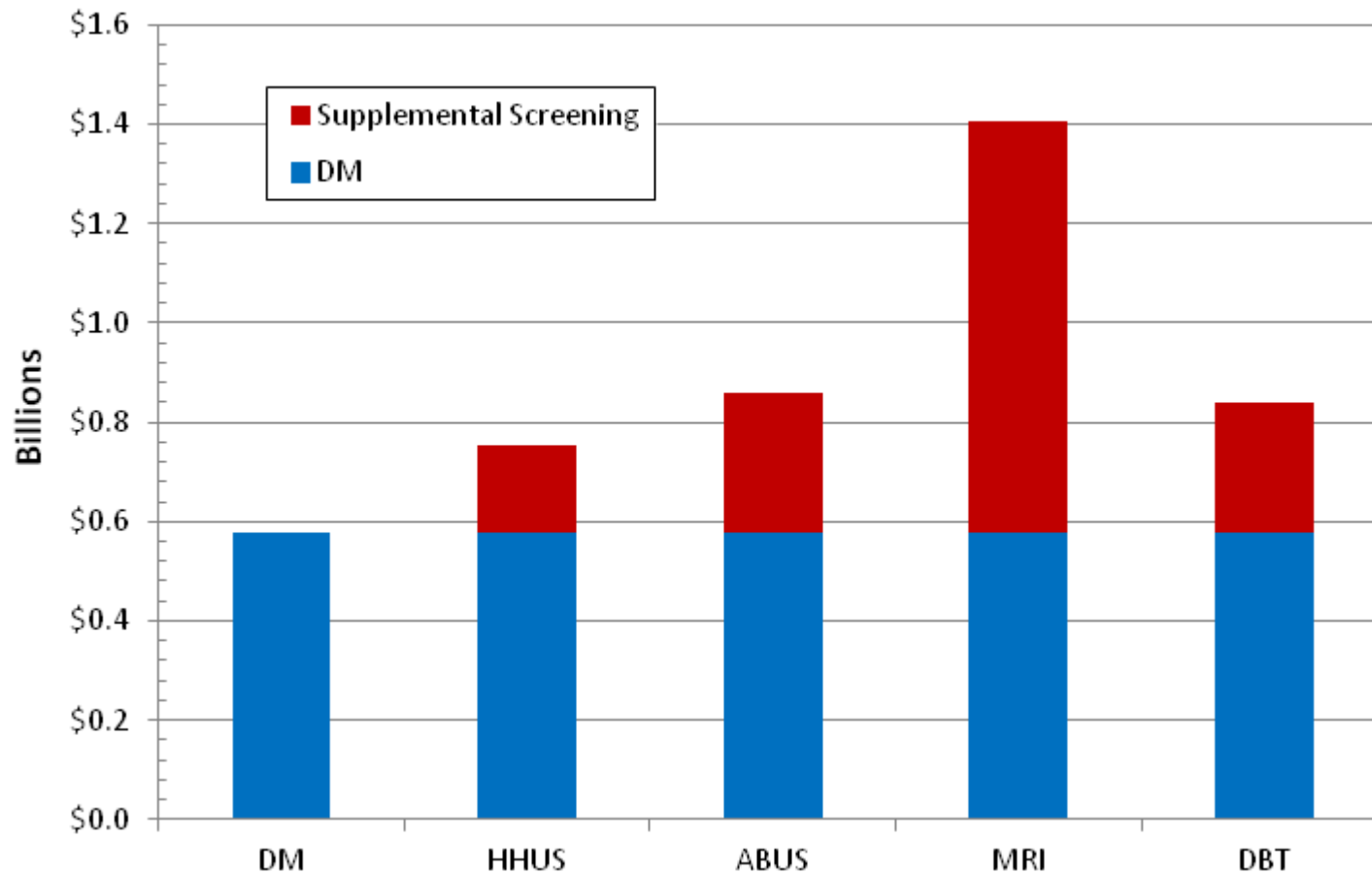


Results: Supplemental Screening (Overall Population)

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 NE (DM+Supplemental)



Impact of MRI Supplemental Screening (Extremely Dense Only)

Risk	# Patients	Incremental \$
Low	96,138	\$63,168,296
Moderate	108,481	\$72,288,785
High	23,566	\$15,919,515
TOTAL	228,186	\$151,376,597

