Comparative Effectiveness of Combined Digital Mammography and Tomosynthesis Screening for Women with Dense Breasts[1]

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Purpose: To evaluate the effectiveness of combined biennial digital mammography and tomosynthesis screening, compared with biennial digital mammography screening alone, among women with dense breasts.

Materials and Methods: An established, discrete-event breast cancer simulation model was used to estimate the comparative clinical effectiveness and cost-effectiveness of biennial screening with both digital mammography and tomosynthesis versus digital mammography alone among U.S. women aged 50–74 years with dense breasts from a federal payer perspective and a lifetime horizon. Input values were estimated for test performance, costs, and health state utilities from the National Cancer Institute Breast Cancer Surveillance Consortium, Medicare reimbursement rates, and medical literature. Sensitivity analyses were performed to determine the implications of varying key model parameters, including combined screening sensitivity and specificity, transient utility decrement of diagnostic work-up, and additional cost of tomosynthesis.

Results: For the base-case analysis, the incremental cost per quality-adjusted life year gained by adding tomosynthesis to digital mammography screening was $53 893. An additional 0.5 deaths were averted and 405 false-positive findings avoided per 1000 women after 12 rounds of screening. Combined screening remained cost-effective (less than $100 000 per quality-adjusted life year gained) over a wide range of incremental improvements in test performance. Overall, cost-effectiveness was most sensitive to the additional cost of tomosynthesis.

Conclusion: Biennial combined digital mammography and tomosynthesis screening for U.S. women aged 50–74 years with dense breasts is likely to be cost-effective if priced appropriately (up to $226 for combined examinations vs $139 for digital mammography alone) and if reported interpretive performance metrics of improved specificity with tomosynthesis are met in routine practice.

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Mammography remains the only screening test proven to decrease mortality from breast cancer (1). The U.S. Preventive Services Task Force currently recommends routine biennial screening for women 50–74 years old (2). However, mammography is less accurate in women with dense breasts for whom cancers may be masked by overlapping breast tissue (3,4). Moreover, dense breasts compared with average-density breasts are associated with a moderate to high relative risk (1.2–2.3) for developing breast cancer, independent of the masking effect (5).

Given the limitations of mammography and the increased cancer risk among women with dense breasts, there is a strong advocacy push for mandatory breast density reporting directly to women with dense breasts. As of July 2014, 19 states have enacted laws that require women to be told that they have dense breasts at mammography and that they may benefit from supplemental screening (6). Fifteen additional states are considering similar laws, and federal density notification legislation has been introduced. Given that nearly half of the U.S. screening population has dense breasts (4), an increasingly large number of women may be encouraged to consider supplemental screening beyond conventional mammography.

Nevertheless, the type of supplemental screening, if any, that should be recommended for women with dense breasts is currently unclear. The sensitivity for detecting cancer in dense breast tissue is improved with digital mammography over screen-film mammography (3), and digital mammography now represents more than 90% of the mammography market in the United States (7). However, two-dimensional image interpretation is still influenced by the masking effect caused by dense tissue overlying cancers. Supplemental screening ultrasonography (US) may increase cancer detection in women with dense breasts and at least one other risk factor, but often at the expense of more false-positive findings and benign biopsy results (8). Screening magnetic resonance (MR) imaging is the most sensitive breast imaging test, but it is also more expensive, requires intravenous contrast material injection, and is currently reserved for screening women with at least 20%–25% lifetime cancer risk (9).

Digital breast tomosynthesis, in contrast to US and MR imaging, may offer operational and ease-of-use advantages, since it is an integrated part of newer-generation mammography units (10). With tomosynthesis, mammographic projections are acquired at different angles to generate a three-dimensional image of the breast during the standard mammographic compression (11). It may be of particular interest for evaluating women with dense breasts, since it partially overcomes the masking effect seen with mammography (12). Two European prospective, population-based screening studies and one United States–based retrospective analysis have shown that adjunct tomosynthesis increases cancer detection

Advances in Knowledge

- Combined biennial digital mammography and tomosynthesis, compared with biennial digital mammography alone, for U.S. women aged 50–74 years with dense breasts would avert one additional breast cancer death per 2000 women screened.
- Combined biennial digital mammography and tomosynthesis, compared with biennial digital mammography alone, for U.S. women aged 50–74 years with dense breasts would avert 405 false-positive screening examination findings per 1000 women screened.
- Adding tomosynthesis to biennial digital mammography screening approaches the cost-effectiveness threshold (cost of less than $100 000 per quality-adjusted life year) for U.S. women aged 50–74 years with dense breasts, even with no improvement in the sensitivity of combined screening and moderate improvement in specificity.
- The cost-effectiveness of combined biennial screening for U.S. women aged 50–74 years with dense breasts is most sensitive to the additional cost of tomosynthesis.

Implications for Patient Care

- Combined biennial digital mammography and tomosynthesis screening is likely to decrease the number of false-positive findings and increase the number of cancers detected in women aged 50–74 years with dense breasts, compared with biennial digital mammography alone.
- Compared with biennial digital mammography alone, combined biennial digital mammography and tomosynthesis screening is likely to improve outcomes at reasonable additional cost for U.S. women aged 50–74 years with dense breasts.

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Abbreviations:
BCSC = Breast Cancer Surveillance Consortium
BI-RADS = Breast Imaging Reporting and Data System
CPT = Current Procedural Terminology
ICER = incremental cost-effectiveness ratio
QALY = quality-adjusted life year

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rates while decreasing recall rates (13–15). Moreover, tomosynthesis, which obtained U.S. Food and Drug Administration approval in 2011, is quickly diffusing into community practice with sparse data to guide best practices in U.S. populations (16).

We evaluated the comparative effectiveness of combined biennial digital mammography and tomosynthesis screening, compared with biennial digital mammography screening alone, among women with dense breasts. Our analysis was intended to provide additional information and highlight the variables most likely to influence the ultimate economic effect of incorporating tomosynthesis into routine U.S. breast cancer screening practices.

Materials and Methods

This study was supported in part by the National Cancer Institute and in part by a Radiology Research Academic Fellowship, co-sponsored by GE Healthcare (Waukesha, Wis) and the Association of University Radiologists. The sponsors had no role in the study concept, study design, data analysis, interpretation, or reporting of the results. The authors had full control of the data and information submitted for publication.

By using a discrete-event breast cancer simulation model (17), we projected the population-level effects of adding tomosynthesis to digital mammography screening. Specifically, we compared biennial combined screening with biennial mammography screening for women aged 50–74 years with dense breasts, as biennial mammography screening reflects U.S. Preventive Services Task Force recommendations (2). We modified our model to study only the U.S. subpopulation of women with heterogeneously dense or extremely dense breasts at mammography. For our screening scenarios, all women underwent mammography alone at age 50 (breast density can be determined only after obtaining a baseline mammogram) and then either mammography alone or in combination with tomosynthesis starting with their first follow-up visit at age 52 and thereafter through age 74. We assumed full screening adherence and optimal treatment for every patient in the event of cancer detection. Health care costs and benefits, measured in terms of quality-adjusted life years (QALYs), were discounted 3% annually (18). We performed sensitivity analyses to explore the implications of varying key parameters.

Model Overview

The model, developed by the University of Wisconsin in collaboration with the National Cancer Institute Cancer Intervention and Surveillance Modeling Network, is used to explore ramifications of alternative programs of breast cancer screening and treatment (17) (Appendix E1 [online]). Briefly, this model simulates the life histories of women in the U.S. population by using four interacting processes: breast cancer natural history, detection, treatment, and competing-cause mortality. The model is calibrated on the basis of real-world observations, including U.S. stage-specific breast cancer incidence and mortality (19–21). Treatment effectiveness in the model is a function of age, estrogen receptor status, calendar year, and stage at diagnosis. Women may die of breast cancer or other causes. The model is based on continuous-time tumor growth and accounts for overdiagnosis by allowing a proportion of early-stage breast cancer cases that do not lead to breast cancer–related death (17). The same model was used to determine the cost-effectiveness of digital mammography for breast cancer screening in the United States in 2008 (22) and was one of six models used to update the U.S. Preventive Services Task Force screening recommendations in 2009 (2).

Model Parameter Inputs

The National Cancer Institute–funded Breast Cancer Surveillance Consortium (BCSC) provided breast density and digital mammography performance measures for the model. The population served by the BCSC has been shown to be comparable to the U.S. population (23). Each registry prospectively collects patient-level data from community radiology facilities, including the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) breast density categorical assessments, imaging assessments, and overall recommendations (24). Breast cancer diagnoses and tumor characteristics are available through data linkages to regional Surveillance, Epidemiology, and End Results programs, state tumor registries, and pathology databases (25).

With BI-RADS, breast density is classified into four subjective categories by the interpreting radiologist: almost entirely fat, scattered fibroglandular densities, heterogeneously dense, or extremely dense. As breast density reporting legislation does not differentiate between the two higher-density categories, we consider women with dense breasts to have either heterogeneously dense or extremely dense breasts. Women's breast density can decrease with menopause; however, we assumed that the breast density category assigned at age 50 years (the average age of menopause) remained constant over the remainder of a woman's life.

We specified the prevalence of dense breasts by age and the relative risk of breast cancer according to density among U.S. women on the basis of previously published BCSC data (Table 1) (26,27). We determined the overall sensitivity and specificity for digital mammography, stratified by breast density and age, by fitting logistic regression models to data from nearly 2 million BCSC examinations performed in 2001–2008 (28). We incorporated digital mammography performance characteristics among women 50–74 years of age with dense breasts who underwent biennial screening and for whom 2-year follow-up data were available (Table 1). The BCSC has only recently started collecting data regarding tomosynthesis, so performance data were not available for use at the time of modeling. We therefore estimated base-case combined mammography and tomosynthesis performance characteristics from the published literature. Two European population-based screening trials and one U.S. retrospective analysis have demonstrated statistically significant improvements in recall rates and

Table 1

Screening Population and Imaging Performance Characteristics

Parameter	Base-Case Value	Source
Prevalence of dense breasts in U.S. women (≥50 y)		
Heterogeneously dense (category 3)	0.35	Reference 26
Extremely dense (category 4)	0.05	Reference 26
Relative risk of breast cancer according to density (category 2, scattered fibroglandular, as referent group)		
Heterogeneously dense (category 3)	1.43	Reference 27
Extremely dense (category 4)	1.85	Reference 27
Biennial digital mammography performance characteristics in dense breasts		
Sensitivity*	0.77	BCSC
Specificity*	0.88	BCSC
Biennial combined tomosynthesis with digital mammography performance characteristics		
Sensitivity	0.80 (0.77–0.83)	Reference 14
Specificity	0.92 (0.88–0.95)	Reference 14

Note.—Numbers in parentheses are ranges.

* Digital mammography sensitivity and specificity were calculated with a 24-month follow-up period and weighted according to prevalence of women with heterogeneously dense versus extremely dense breasts.

cancer detection when tomosynthesis is added to digital mammography screening among women at least 50 years old (13–15). We chose the Oslo screening trial to estimate base-case sensitivity and specificity for combined biennial screening, as it was the only study in which figures were provided for false-positive and false-negative screening results in an interim analysis (Table 1) (14). To be conservative, we used the combined Oslo screening performance values as the best-case performance scenario and chose more moderately improved screening performance values for our base-case scenario. We varied performance characteristics for combined biennial screening widely in sensitivity analyses.

Costs

We included age-specific average costs for breast cancer screening, diagnosis, and treatment in our model (Table 2). For mammography screening and diagnostic work-up costs, we used average Medicare reimbursement rates (29) and resource utilization figures from a managed care registry of the BCSC, stratified by patient age and diagnostic result (false-positive screening findings, true-positive screening findings, and clinically detected cancers) (28). We also assigned age-specific average costs for women undergoing additional invasive diagnostic procedures, including image-guided biopsy and surgical excision (10.6% of all positive BCSC screening examination findings). For treatment costs, we used the most recently published average costs stratified by cancer stage (30).

The average cost of adjunct tomosynthesis is based on reported out-of-pocket charges for women at private radiology practices ($50), since there was no direct Current Procedural Terminology (CPT) code at the time of modeling (16). This figure is also consistent with average reimbursement from payers for accessory CPT code 76499, an unlisted diagnostic radiographic procedure, which was also commonly used for adjunct tomosynthesis reimbursement at the time of modeling. Since the cost of tomosynthesis is currently in flux, we varied it widely in sensitivity analyses. We adjusted all costs to 2013 U.S. dollars (34).

Utilities

We used age-specific and stage-specific health state utility values for healthy women and women with breast cancer derived from published EuroQol-5D survey results (Table 2) (31). These health utilities include reductions for treatment morbidity and loss of quality of life for patients with breast cancer (32). We also included small, transient reductions in utility for women undergoing screening and those undergoing diagnostic work-up after positive screening findings (33). The utility reduction from diagnostic work-up varied widely in sensitivity analyses. Since tomosynthesis is completed during standard mammographic compression and requires only a few additional seconds, no further reduction in utility was assumed for adjunct tomosynthesis.

Sensitivity Analyses

We performed multiway sensitivity analyses to explore the implications of varying key parameters, including combined tomosynthesis and digital mammography screening sensitivity and specificity, cost of adjunct tomosynthesis, and transient utility reduction for diagnostic work-up after positive screening (Tables 1, 2). We also performed a sensitivity analysis to compare biennial combined screening to annual digital mammography screening by using BCSC digital mammography performance characteristics among women 50–74 years of age with dense breasts.

Results

Cost-Effectiveness Analysis

The cost-effectiveness of adding tomosynthesis to biennial digital mammography screening for women aged 50–74 years with dense breasts is summarized in Table 3. For our base-case analysis, combined screening demonstrated a total discounted cost of $4440 (compared with $4091 for mammography alone), 20.652 life-years (compared with 20.647 life-years for mammography alone), and 16.814 QALYs per woman screened (compared with 16.807 QALYs for mammography alone). The incremental cost per life-year gained for combined screening compared with

Table 2

Costs and Utilities

Parameter	Base-Case Value	Source(s)
Costs*		
Screening digital mammography examination	$139	Reference 29
Adjunct screening tomosynthesis examination†	$50 ($0–$139)	Reference 16
Diagnostic work-up for true-positive screening findings or clinically detected cancer		Reference 28
Age of 50–64 y	$2105	
Age of 65–74 y	$2116	
Diagnostic work-up for false-positive screening findings		Reference 28
Age of 50–64 y, imaging only	$138	
Age 50–64 y, imaging and invasive procedure(s)	$1461	
Age 65–74 y, imaging only	$138	
Age 65–74 y, imaging and invasive procedure(s)	$1468	
Treatment according to cancer stage		Reference 30
Stage I, in situ: initial year	$13 376	
Stage I, in situ: last year	$36 205	
Stage II, local: initial year	$13 376	
Stage II, local: last year	$36 205	
Stage III, regional: initial year	$25 290	
Stage III, regional: last year	$42 855	
Stage IV, distant: initial year	$39 058	
Stage IV, distant: last year	$60 019	
Age-specific utilities for healthy and cancer states		
Healthy		References 31, 32
Age of 50–59 y	0.845	
Age of 60–69 y	0.812	
Age of 70–79 y	0.788	
Age of 80+ y	0.762	
Stage I, in-situ cancer (first year, later years)		References 31, 32
Age of 50–59 y	0.764, 0.845	
Age of 60–69 y	0.734, 0.812	
Age of 70–79 y	0.712, 0.788	
Age of 80+ y	0.689, 0.762	
Stage II, local cancer (first year, later years)		References 31, 32
Age of 50–59 y	0.715, 0.828	
Age of 60–69 y	0.687, 0.796	
Age of 70–79 y	0.667, 0.772	
Age of 80+ y	0.645, 0.747	
Stage III, regional cancer (first year, later years)		References 31, 32
Age of 50–59 y	0.636, 0.765	
Age of 60–69 y	0.611, 0.735	
Age of 70–79 y	0.593, 0.713	
Age of 80+ y	0.574, 0.690	
Stage IV, distant metastases (first year, later years)		References 31, 32
Age of 50–59 y	0.636, 0.703	
Age of 60–69 y	0.611, 0.676	
Age of 70–79 y	0.593, 0.656	
Age of 80+ y	0.574, 0.634	

Table 2 (continues)

mammography screening was $70 500. The incremental cost per QALY gained (or the incremental cost-effectiveness ratio [ICER]) of combined screening compared with mammography screening was $53 893. In sensitivity analyses, the ICER was most sensitive to the cost of tomosynthesis, followed by combined screening specificity, combined screening sensitivity, and transient utility reduction from diagnostic work-up after positive screening findings (Figure).

Our base-case analysis involved more modest performance improvements with combined screening (sensitivity of 0.80 and specificity of 0.92, compared with digital mammography, with sensitivity of 0.77 and specificity of 0.88) than what was observed in the Oslo study (sensitivity of 0.83 and specificity of 0.95). When we increased the absolute improvement in sensitivity of combined screening to those values observed in the Oslo study, combined screening was slightly more cost-effective (ICER of $37 548, cost-effectiveness threshold of $100 000). We also calculated an ICER for the scenario with no incremental improvement in sensitivity after adding tomosynthesis to mammography screening. In this situation, combined screening approached the cost-effectiveness threshold, owing to moderately improved specificity alone (ICER of $104 447). When we increased absolute improvement in specificity of combined screening to what was observed in the Oslo trial, combined screening was very cost-effective (ICER of $33 749). When we decreased the absolute improvement in specificity of combined screening to be minimal (from 0.92 to 0.90, with mammography specificity of 0.88), combined screening remained cost-effective (ICER of $75 846).

In a best-case performance scenario of marked improvements in sensitivity and specificity as seen in the Oslo trial, combined screening had an incremental cost per QALY of $26 107. In a worst-case performance scenario of no improvements in sensitivity and specificity, combined screening had an incremental cost per QALY of $792 264. Varying the amount of

Table 2 (continued)

Costs and Utilities

Parameter	Base-Case Value	Source(s)
Utility reductions for screening and diagnostic work-up		Reference 33
Screening attendance	0.006 for 1 wk	
Diagnostic work-up phase	0.105 for 5 wks‡	

* All costs were adjusted to 2013 U.S. dollars.

† Numbers in parentheses are the range.

‡ The utility reduction for diagnostic work-up was varied in sensitivity analyses; range, 0–0.105.

transient utility reduction from diagnostic work-up with base-case performance parameters did not have a large effect on the relative cost-effectiveness of combined screening (ICER of $85 658 for no transient utility reduction). Finally, increasing the cost of adjunct tomosynthesis did not affect the relative cost-effectiveness of combined screening until the added cost of tomosynthesis exceeded $87 (for a total screening cost of $226).

Additional Deaths and False-Positive Findings Averted

In our base-case analysis, with moderate improvements in both sensitivity and specificity after adding tomosynthesis to biennial digital mammography screening for women aged 50–74 years with dense breasts, 0.5 breast cancer-related deaths were averted and an additional 405 false-positive findings averted per 1000 women after 12 screening rounds (Table 4). With marked improvements in both sensitivity and specificity, as seen in the Oslo trial, combined biennial screening resulted in one additional breast cancer–related death averted and an additional 727 false-positive findings averted per 1000 women compared with biennial mammography screening alone. In our sensitivity analysis, we compared the base-case biennial combined screening scenario to annual digital mammography screening for women aged 50–74 years with dense breasts and found that biennial combined screening prevented an additional 1723 false-positive findings per 1000 women; however, annual digital mammography screening averted 1.7 more breast cancer–related deaths per 1000 women after 12 rounds of screening.

Discussion

In light of new breast density reporting legislation and the immediate need for guidance on supplemental screening beyond conventional mammography for women with dense breasts, we provided estimates of the clinical effect and cost-effectiveness of adjunct tomosynthesis screening on the basis of currently available evidence. Our analysis suggested that adding tomosynthesis to biennial digital mammography screening for women aged 50–74 years with dense breasts was likely to improve health outcomes at a reasonable cost relative to biennial digital mammography screening alone. Our findings were robust over a range of assumptions, including suboptimal combined screening performance characteristics.

In contrast to supplemental screening US and MR imaging, which are associated with increases in both cancer detection and false-positive findings, adjunct tomosynthesis has been shown to increase cancer detection while decreasing false-positive findings (11,13,14). For our base-case analysis, combined digital mammography and tomosynthesis screening averted one additional breast cancer–related death per approximately 2000 women screened (4% added mortality rate reduction compared with digital mammography screening alone) after 12 rounds of biennial screening. In comparison, a meta-analysis of prior randomized controlled trials demonstrated that one breast cancer–related death was averted per 1339 women aged 50–59 years invited for mammography screening after five rounds of biennial screening (2).

The decrease in false-positive screening findings after adding tomosynthesis is a major contributor to the cost-effectiveness of combined screening. Our study suggests that adding tomosynthesis at the time of mammography screening has the potential to decrease the number of unnecessary diagnostic work-ups and invasive procedures that result from false-positive screening findings. The reduction of these known harms of mammography may serve to shift current opinions regarding the balance between the benefits and harms of breast cancer screening.

This cost-effectiveness analysis was challenging for a number of reasons. Since tomosynthesis is a relatively new technology, its use in the U.S. population has not been well studied. To date, no randomized controlled trials on the comparison of combined screening with mammography and tomosynthesis versus mammography alone have been performed. Detailed population-based performance data for tomosynthesis are currently limited to two prospective, nonrandomized trials performed in Europe. Both the Screening with Tomosynthesis or Mammography—or STORM—trial, based in Italy, and the Oslo trial, based in Norway, suggested performance improvements with adjunct tomosynthesis, with increased cancer detection rates and decreased recall rates (13,14). A recent retrospective analysis of aggregate data from multiple U.S. facilities demonstrated comparable improvements in overall cancer detection rate and recall rate to those of European studies, but without detailed data needed to calculate raw sensitivity and specificity values for combined screening that could be used as model input parameters (15).

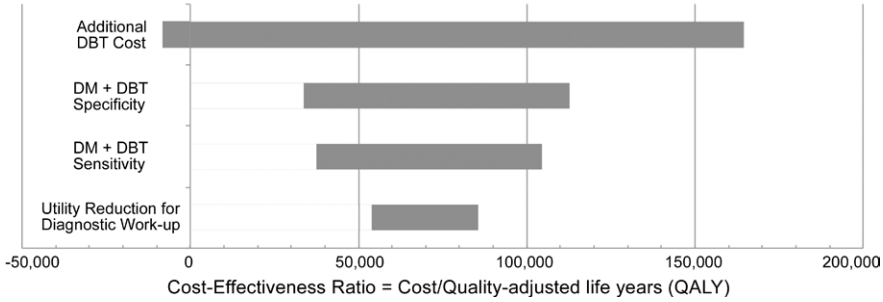
While our analysis focused on the subpopulation of women with dense breasts, the Oslo data were not stratified by breast density. However, a recent study in the United States demonstrated increasing improvements

Table 3

Cost-Effectiveness Analysis Results

Scenario Description	Sensitivity of Digital Mammography and Tomosynthesis	Specificity of Digital Mammography and Tomosynthesis	Additional Tomosynthesis Cost ($)	ICER (cost per life year gained) ($)	ICER (cost per QALY gained) ($)
Base case: moderately improved sensitivity and specificity with combined digital mammography and tomosynthesis					
Base-case tomosynthesis cost	0.80	0.92	50	70 500	53 893
No additional tomosynthesis cost	0.80	0.92	0	−10 805	−8260
Screening cost doubled by tomosynthesis	0.80	0.92	139	215 222	164 527
Markedly improved sensitivity with combined digital mammography and tomosynthesis					
Markedly improved specificity	0.83	0.95	50	33 602	26 107
Moderately improved specificity	0.83	0.92	50	40 491	37 548
Minimally improved specificity	0.83	0.90	50	45 105	48 033
No improvement in specificity	0.83	0.88	50	49 701	62 155
Moderately improved sensitivity with combined digital mammography and tomosynthesis					
Markedly improved specificity	0.80	0.95	50	57 471	33 749
Minimally improved specificity	0.80	0.90	50	79 228	75 846
No improvement in specificity	0.80	0.88	50	87 919	112 584
No improvement in sensitivity with combined digital mammography and tomosynthesis					
Markedly improved specificity	0.77	0.95	50	321 675	51 630
Moderately improved specificity	0.77	0.92	50	400 685	104 447
Minimally improved specificity	0.77	0.90	50	453 618	202 674
No improvement in specificity	0.77	0.88	50	506 332	792 264

Note.—All scenarios are for biennial screening of women aged 50–74 years with dense breasts who underwent both digital mammography and digital breast tomosynthesis. Digital mammography sensitivity in dense breasts = 0.77; digital mammography specificity for dense breasts = 0.88; digital mammography cost = $139 in 2013 dollars. ICER refers to the incremental cost-effectiveness ratio of digital mammography and tomosynthesis screening versus digital mammography screening alone.



Graph depicts sensitivity analysis for the cost-effectiveness of adding digital breast tomosynthesis *(DBT)* to standard biennial digital mammography *(DM)* screening in women aged 50–74 years with dense breasts. Additional cost of digital breast tomosynthesis ranged from $0 to $139; digital mammography with tomosynthesis specificity ranged from 0.88 to 0.95; digital mammography with tomosynthesis sensitivity ranged from 0.77 to 0.83; and transient utility reduction for diagnostic work-up after positive screening findings ranged from 0 to 0.105.

in adjunct tomosynthesis performance with increasing breast density categories (35). Thus, our use of combined screening performance characteristics for all women, regardless of breast density, may undervalue the effectiveness of adjunct tomosynthesis for women with dense breasts. Nevertheless, we believed that the Oslo parameters represented the best available estimates of adjunct tomosynthesis effectiveness in population-based screening at the time of our analysis.

Another challenging aspect was determining an average cost of adjunct tomosynthesis, as there was no direct CPT code at the time of modeling. We chose an average cost of $50 on the basis of current out-of-pocket charges among private practices in different regions of the country and the average reimbursement for accessory CPT code 76499, an unlisted diagnostic radiographic procedure code accepted by some payers at the time of modeling (16). In sensitivity analyses, the combined screening strategy remained cost-effective until the added cost of tomosynthesis increased to $87, effectively increasing the cost of screening to $226 (compared with

Table 4

Effects of Biennial Screening Strategies for 12 Rounds of Screening between Ages 50 and 74 Years per 1000 Women

Screening Strategy	No. of Screenings	No. of Breast Cancers Detected	No. of Breast Cancer Deaths	No. of False-Positive Findings
Digital breast tomosynthesis and digital mammography*	10901	208	14.9	856
Digital mammography alone*	10935	202	15.4	1261
Incremental difference	−34	+6	−0.5	−405

* Results are for base-case performance values of digital mammography and digital breast tomosynthesis.

$139 for digital mammography alone). Whether or not adjunct tomosynthesis will be reimbursed below such a threshold value, or at all, remains uncertain.

There were several additional limitations to our study. First, we focused our analysis on biennial screening of women with dense breasts who were 50–74 years of age, since tomosynthesis data were only available for this age group and screening interval; thus, our results were not applicable to women 40–49 years of age or those undergoing annual combined screening. However, we do provide a sensitivity analysis to compare biennial combined screening to annual digital mammography screening for women aged 50–74 years with dense breasts. This analysis demonstrated that biennial combined screening averts a large number of false-positive findings but averts slightly fewer cancer deaths than annual digital mammography screening. Second, we do not stratify our results for women with heterogeneously dense versus extremely dense breasts. This is due to the fact that breast density reporting legislation does not distinguish between these two BI-RADS density categories, and our analysis is meant to be informative to current real-world practice. Third, we did not address increased radiation exposure from tomosynthesis. The added dose, which is equivalent to the dose of a digital mammography examination, still puts combined screening at a total dose lower than the limit for a standard screening examination set by the Mammography Quality Standards Act (36). In addition, the U.S. Food and Drug Administration recently approved imaging software that reconstructs standard mammography images from the three-dimensional tomosynthesis acquisition, negating the need for additional radiation exposure. Finally, we built our model with the assumption that a woman's breast density would not change over time after age 50. This might lead to overestimation of the density at long follow-up times and thus overestimation of the added benefit of tomosynthesis. However, varying breast density in the model would have substantially increased the complexity of the analysis.

Large breast imaging registries, such as those comprising the BCSC and the Population-based Research Optimizing Screening through Personalized Regimens—or PROSPR—consortium, may provide valuable U.S.-based performance data from community practices. In future cost-effectiveness analyses, investigators should consider different density subgroups, breast cancer risks, imaging frequencies, and perspectives. The cost-effectiveness of adjunct tomosynthesis should also be compared directly with those of other potential supplemental screening modalities, including MR imaging and US.

Our analysis, conducted by using currently available data, provides women, physicians, payers, and policymakers in the United States with much-needed information regarding the comparative effectiveness of combined mammography and tomosynthesis screening relative to mammography screening alone. Our results suggest that biennial combined screening for women aged 50–74 years with dense breasts is a cost-effective approach from a federal payer perspective if priced appropriately (below a threshold combined screening cost of $226 vs $139 for digital mammography alone) and if interpretive performance metrics of improved specificity are met in routine practice.

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