Supplementary material

Appendix 1, as supplied by the authors. Appendix to: Cressman S, Mar C, Sam J, et al. The cost-effectiveness of adding tomosynthesis to mammography-based breast cancer screening: an economic analysis. *CMAJ Open* 2021. doi:10.9778/cmajo.20200154.

S1. Cost and outcomes data

a) Screening outcomes

The screening outcomes data included all new screening participants, aged 40-74, who had their index (*i.e.* baseline or first-ever) screening exam with digital mammography between January 1, 2012 and December 31, 2017, inclusive. This time frame was selected to enable comparisons with DM; which displaced analog mammography in 2012. The analysis was restricted to participants who identified as women and were registered in the provincial screening program and health insurance system. The breast screening results (normal *vs.* abnormal) were coded for each exam in the screening data, according to the radiologist's interpretation of the exam.

b) Breast cancer outcomes

Breast cancer outcomes data women who had a history of screening participation through the BC Cancer Breast Screening Program and had a malignant breast cancer diagnosis in the population-based BC Cancer Registry, between January 1, 2007 and December 31, 2016. The BC Cancer registry houses data on the diagnostic characteristics of breast cancer including tumour behaviour, histology, stage and laterality, with regularly updated linkage to provincial vital statistics for date of death. This dataset was used to determine mortality rates after a diagnosis of breast cancer. Breast cancer cases were classified into high- and low-risk subgroups, based on stage and histology fields in the registry data. All *in situ* and Stage I breast cancer according to American Joint Committee on Cancer (AJCC) or tumour/metastasis/node (TNM) staging system, excluding triple negative breast cancer, were sub-grouped as "low-risk". Every other type of breast cancer, including any stage of triple negative breast cancer was assigned to the "high-risk" subgroup.

Table S.1. Breast cancer outcomes and linked resource utilization datasets

	Breast cancer cohort	Resource utilization sub-cohort from linkage between the breast cancer cohort and the screening cohort
n	19,509	809
Mean age (range)	61.0 (36-95)	53.3 (40-73)
Stage		
In situ	3521 (18%)	162 (20%)
I	9658 (49%)	335 (41%)

II	4787 (25%)	224 (28%)
III	1218 (6%)	73 (9%)
IV	325 (2%)	15 (2%)
Receptor status[a]		
Triple negative	1111 (8.9%)	48 (7.6%)
HER2 subgroups		
ER-PR-HER2+	526 (4.19%)	30 (4.8%)
ER+PR+HER2+	796 (5.0%)	55 (8.5%)
ER+PR-HER2+	416 (3.3%)	22 (3.5%)
ER-PR+HER2+	11 (0.1%)	n.r.[b]
ER+PR+HER2-	8494 (67.6%)	441 (70.1%)
ER+PR-HER2-	1125 (9.0%)	30 (4.8%)
ER-PR+HER2-	56 (0.5%)	n.r.
Missing receptor status information	3428 (17.6%)	18 (2.2%)

[a]For invasive breast cancer only

[b]n.r=not reportable, sample sizes less than 10 are not reported

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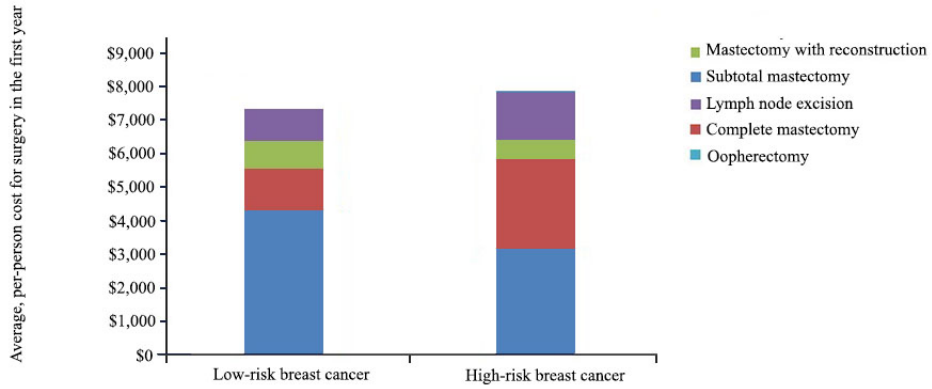
A)



B)

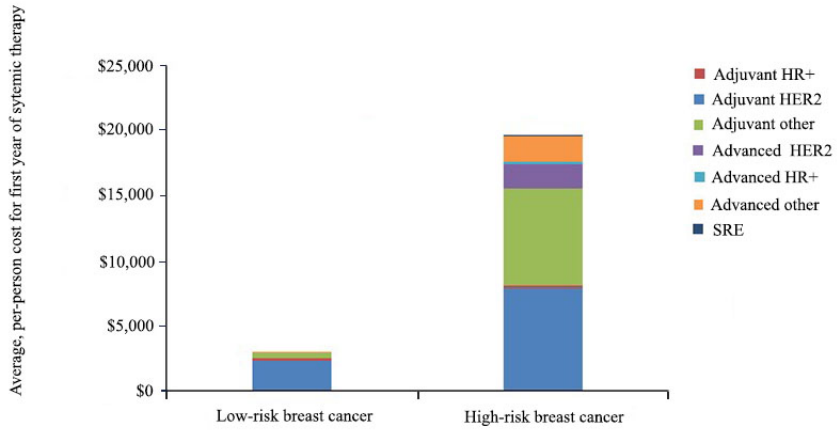


Figure S.1. Year 1 Breast Cancer Treatment costs

S. 2. Transition probabilities

The model is based on an extending markov assumptions to restrict transitions toward direction only. The decision to extend the markov model was made with input from the stakeholder team and the individual odds ratios of cancer incidence and subsequent abnormal results following an abnormal versus normal exam result. Over 662 median days of follow up, the odds of cancer in participants who have had an abnormal exam is higher OR: 16.08 (95%CI:13.56-19.06), than in participants with normal exam results, as is the risk of future abnormal exams (OR=1.24, 95%CI: 1.14 – 1.35); therefore we defined an "ever-abnormal" health state and restrict all transitions from this health state to forward only pathways between subsequent health state transitions. The

rationale for dividing breast cancer into "low-" and "high-risk" health states relate to the available therapies and prognostic risks for treatments.

Transitions from normal or ever-abnormal to low- or high-risk breast cancer, or dead from any health state were non-reversible. The screening and cancer outcomes datasets were used to calculate health state transition probabilities following the index mammogram (*i.e.* the risk that screening participants will have a subsequent abnormal exam result, develop breast cancer, or die from any cause). Transition probabilities that change over time, such as the development of breast cancer or mortality rates, used Weibull regression on time to event data starting from the date of the index screening exam or date of breast cancer diagnosis, respectively. Weibull regression parameters were fit to yield the shape and slope parameters for calculating annual transition probabilities from each non-absorbing health state. For each year following the index screening exam, the annual probability of having an abnormal exam result, developing high or low-risk breast cancer, or dying was calculated from the date of their index screening exam to the date of transition to another health state or December 31, 2016, whichever occurred first.

Table S.2 Transition probabilities and distributions

Parameter	Comparison arm	Initial value	Weibull parameters	Distribution parameters reference
Normal index mammogram (initial)	DBT+DM	0.8260	n/a	95% CI from meta-analysis[1]
	DM alone	0.8050	n/a	n= number of index exams (112,249); r= normal result (90,637)
Subsequent mammogram, Normal to Ever-abnormal transition	DBT+DM	0.0690	n/a	95% CI from meta-analysis[1]
	DM alone	0.0905	n/a	n= number of first subsequent exams (40,019); r= abnormal first subsequent result (3,659)
Normal to Low-risk transition	Same inputs for both study arms	0.0004	n/a	Mean and SE (0.01%)
Normal to High-risk transition	Same inputs for both study arms	0.0009	n/a	Mean and SE (0.01%)
Background mortality	Same inputs for both study arms	0.0024	n/a	n= 174, 000 females in 2017; r=419 female deaths in BC in 2017[2]
Ever-abnormal to Low-risk breast cancer	DBT+DM	0.0507	λ= -5.17 γ= 0.34	Mean and SE(0.16%)
	DM alone	0.0409		
Ever-abnormal to High-risk breast cancer	Same inputs for both study arms	0.0250	λ= -5.37 γ= 0.29	Mean and SE(0.12%)

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Low-risk breast cancer mortality	Same inputs for both study arms	0.0034	λ= -17.73 γ= 1.83	Mean and SE(0.05%)
High-risk breast cancer mortality	Same inputs for both study arms	0.0231	λ= -11.24 γ= 1.25	Mean and SE(0.21%)

[1]Reference to meta-analysis

[2]Mortality rates for females increase every 5 years, population of females in BC in 5-year age groupings between 50 and 89.

S.3. Resource utilization rates and cost analysis

Resource utilization rates for all systemic therapy, radiotherapy treatments and surgery were calculated using administrative data from BC Cancer. Systemic therapy resources were calculated from each milligram of drug administered, pharmacy dispensing and intravenous administration resources after adjusting for protocols that specified co-administration. Use of commercially available diagnostic tests to estimate the risk of recurrence was assumed for any hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) and node-negative breast cancer. Radiotherapy resources were accounted for through the number of fractions delivered and the number of courses of radiotherapy. Radiotherapy resource costing accounted for fixed treatment planning and capital costs, per-patient, per-year with reference to recently published methods (25). For the minority of patients with low-risk breast cancer who were not referred to BC Cancer for radiotherapy or chemotherapy, the cost of a subtotal mastectomy was assumed. It is standard practice in British Columbia that all low-risk breast cancers, including *in situ* cancers are surgically treated. Resources for participants who died of breast cancer were accounted for by assigning a one-time palliative care cost for breast cancer in the last year of life with reference to a recent cost-analysis (26). Accumulation of annual resource utilization rates started from the date of a breast cancer diagnosis to the data of death or the last complete year prior to the date of follow-up, whichever occurred first. Annual per-patient costs were calculated as the product of resource utilization rates multiplied by unit costs for each health state in the model. The additional cost of supplementing DM with DBT was estimated based on the expected equipment, maintenance, and image storage costs, and reimbursement fees published in the schedule from the Medical Services Plan of BC, as detailed in the supplementary methods. Unit costs were calculated in 2019 Canadian dollars using the consumer price index values for inflation on July 1st, 2019, from the Bank of Canada.

Table S.3 Screening exam unit costs

UNIT	Type of sub-unit	Sub-unit description	Cost per sub-unit	Fee reference[1]
DM (Routine screening exam using digital mammography, comparator arm of the analysis)	Base rate for screening mammography, includes patient education and covers payment to physicians and facility		$124.86	Alberta Health Service fee Code X 27C-E
TOTAL UNIT COST for DM			$124.86	
DBT (Routine screening exam using digital mammography with adjunct DBT, intervention arm of the analysis)	Base rate for screening mammography, includes patient education and covers payment to physicians and facility		$124.86	Alberta Health Service fee Code X 27C-E
	Additional fee modifier for provision of adjunct tomosynthesis		$43.99	Alberta Health Service fee Code TOMO fee modifier for diagnostic or therapeutic use
TOTAL UNIT COST for DM + DBT			$168.85	

[1]Alberta Health Services reimbursement schedule (https://www.albertadoctors.org/fee-navigator/hsc/X27C)

Table S.4 Diagnostic evaluation costs for the first year following an abnormal exam

Sub Unit	Sub -unit cost	Resource utilization rate	Weighted cost
Diagnostic mammogram	$144	0.94	$135
Ultrasound	$60	0.67	$46
Fine Needle Aspiration	$710	0.10	$71
Core Biopsy	$840	0.16	$134
Open Biopsy with localization	$984	0.02	$20
Open Biopsy without localization	$975	0.03	$29
Surgical Consult	$115	1.0	$115
Total average per-person cost			$550

Table S.5 Surgical Treatment unit costs, according to Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures codes

Unit (CCP Code)	Subunit	Fee	Reference

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Unilateral complete mastectomy (9712)	Hospital facility and administration costs	$4,298.28	Case costing for breast cancer surgery[1]
	Professional fee to surgeon	$638.71	MSP V07472, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$327.62	MSP 1173, 1108, assume two hours for surgery and one inpatient consultation[2]
	Pathology professional fee	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents[2]	$243.00	Reagents[2]
	Total	$5,931.00	
Bilateral simple extended mastectomy (9713)	Hospital facility and admin costs	$4,298.28	Case costing for breast cancer surgery[1]
	Professional fee to surgeon	$1,112.84	MSP V07472, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$466.06	MSP 1173, 1108, assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$292.86	MSP 94010; initial consultation
	Pathology supplies and reagents	$486.00	Reagents[2]
	Total	$6,933.00	
Mastectomy, radical modified; complete mastectomy with excision of lymph nodes (9714)	Hospital facility and admin costs	$4,298.28	Case costing for breast cancer surgery[1]
	Professional fee to surgeon	$638.71	MSP V07472, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$327.62	MSP 1173, 1108, assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$243.00	Reagents[2]
	Total	$5,931.00	
	Hospital facility and admin costs	$8,287.79	Case costing for breast cancer surgery,

Unilateral subcutaneous mastectomy with implant prosthesis (9721)			including immediate reconstruction[1]
	Professional fee to surgeon	$1,558.84	MSP V07498, 71015, 71008, P61045, P91047; assume three inpatient consultations[2]
	Surgeon assistant	$345.82	MSP 13194, 00196
	Anesthetist	$466.06	MSP 1173, 1108; assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$243.00	Reagents[2]
	Total	$11,047.94	
Other unilateral subcutaneous mastectomy (9722)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$822.15	MSP V07472, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$345.82	MSP 13194, 00196
	Anesthetist	$302.17	MSP 1173, 1108; assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$243.00	Reagents[2]
	Total	$6,157.85	
Excision of nipple (9725)	Hospital facility and admin costs	$464.61	Reference to CIHI case costing[1]
	Professional fee to surgeon	$391.88	MSP V07470, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$221.94	MSP 13194, 00196
	Anesthetist	$132.48	MSP 1173, 1108; assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$243.00	Reagents[2]
	Total	$1,600.34	

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Subtotal Mastectomy (9728)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$467.03	MSP V07473, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$303.24	MSP 13194, 00196
	Anesthetist	$327.62	MSP 1173, 1108; assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$243.00	Reagents[2]
	Total	$5,786.44	
Unilateral Mastectomy (9731)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$791.99	MSP V07472, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$345.82	MSP 13194, 00196
	Anesthetist	$327.62	MSP 1173, 1108; assume three hours for surgery and one inpatient consultation[2]
	Total	$5,763.71	
Skin-sparing mastectomy, unilateral, with removal of nipple (97121)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$1,136.22	MSP V07498, 6157, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$345.82	MSP 13194, 00196
	Anesthetist	$396.84	MSP 1173, 1108; assume three hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$243.00	Reagents[2]
	Total	$6,566.59	
Excision of axillary or sentinel lymph node (5213 or 5220)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$668.22	MSP V07479, 71015, 71008; assume three inpatient consultations[2]

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	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$189.18	MSP 1173, 1108; assume one hour in surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$50.00	Reagents[2]
	Total	$5,629.07	
Extended lymph node dissection (5285)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$668.22	MSP V07474, 71015, 71008; assume three inpatient consultations[2]
	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$189.18	MSP 1173, 1108; assume one hour in surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$50.00	Reagents[2]
	Total	$5,629.07	
Removal of both ovaries and tubes during the same operation (7741)	Hospital facility and admin costs	$4,298.28	Assume costs and length of stay are similar to breast cancer surgery[2]
	Professional fee to surgeon	$522.61	MSP V4003; assume three inpatient consultations[2]
	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$358.02	MSP 1175, 1108; assume two hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$50.00	Reagents[2]
	Total	$5,652.30	
Laproscopic bilateral salpingoectomy and oophorectomy (7751)	Hospital facility and admin costs	$4,298.28	Reference to CIHI case costing[1]
	Professional fee to surgeon	$1,145.38	MSP PC04709, 71015, 71008; assume three inpatient consultations[2]

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	Surgeon assistant	$276.96	MSP 13194, 00196
	Anesthetist	$358.02	MSP 1175, 1108 assume two hours for surgery and one inpatient consultation[2]
	Pathologist	$146.43	MSP 94010; initial consultation
	Pathology supplies and reagents	$50.00	Reagents[2]
	Total	$6,275.07	

[1]Pataky and Balisky, 2016 (38)
[2]Expert opinion

Table S.6 Systemic therapy drug unit costs

	Cost per mg (2019 CDN $)	Reference, year prices reported[1]	Patent expiry
Anastrozole	1.27	10161, 2018	Expired
Bevacizumab	3.85	10158, 2019	2019
Capecitabine	0.0035	10055, 2015	Expired
Chlondronate	0.005	ODB[2], 2019	Expired
Cyclophosphamide	0.09	10127, 2018	Expired
Docetaxel	11.42	10127, 2018	Expired
Doxorubicin	4.87	10127, 2018	Expired
Epirubicin	0.39	10127, 2018	Expired
Eribulin	540.00	10005, 2012	Estimated to expire between 2019-2023
Exemestane	0.05	10150, 2019	Expired
Everolimus	20.13	10150, 2019	2019
Flourouracil	0.03	10127, 2018	Expired
Goserelin	111.49	ODB[2], 2019	Expired
Letrozole	0.55	10161, 2018	Expired
Leuprolide	39.60	10149, 2019	Expired
Methotrexate	0.32	10095, 2017	Expired
Paclitaxel	10.00	10127, 2018	Expired
Palbociclib	2.02	10150, 2019	Estimated to expire in 2023
Pamidronate	2.89	ODB[2], 2018	Expired
Pertuzumab	7.93	10127, 2018	Estimated to expire in 2023
Pembrolizumab	44.00	10153, 2018	Estimated to expire in 2026
Ribociclib	0.50	10112, 2018	Estimated to expire in 2029
Tamoxifen	0.02	10150, 2019	Expired
Trastuzumab	6.43	10127, 2018	Expired
Trastuzumab Emtansine	25.08	10024, 2014	Estimated to expire in 2020

[1]pCODR review number, available at: https://www.cadth.ca/pcodr/find-a-review
[2]ODB, Ontario Drug Benefit formulary: https://www.formulary.health.gov.on.ca/formulary

S.4. Cost-effectiveness

The probabilistic sensitivity analysis used 100,000 Monte Carlo simulations to sample the probability distributions for all the parameters in the model simultaneously. Uncertainty from the data on costs used Gamma distributions and uncertainty around the transition probabilities and health utility data used Beta distributions. The parameters were set so that the 95% central interval of the resulting distribution matched the 95% confidence interval from the published literature.

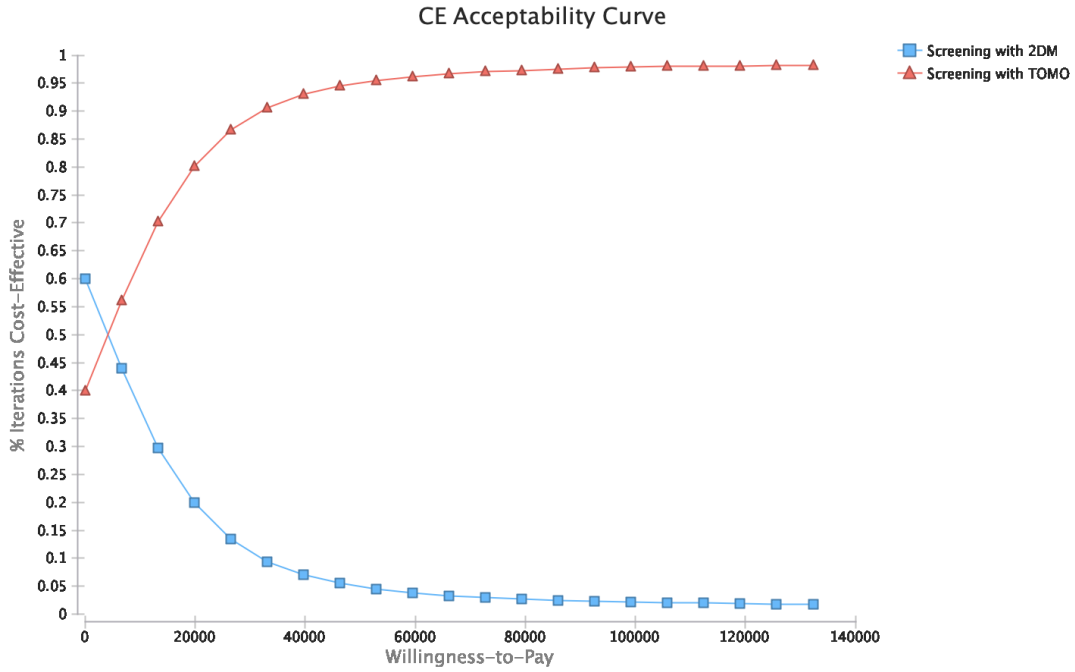

Figure S.2. Cost-Effectiveness Acceptability Curve from the Probabilistic Sensitivity Analysis comprised of 100, 000 iterations of Monte Carlo simulations with simultaneous sampling of all parameter distributions

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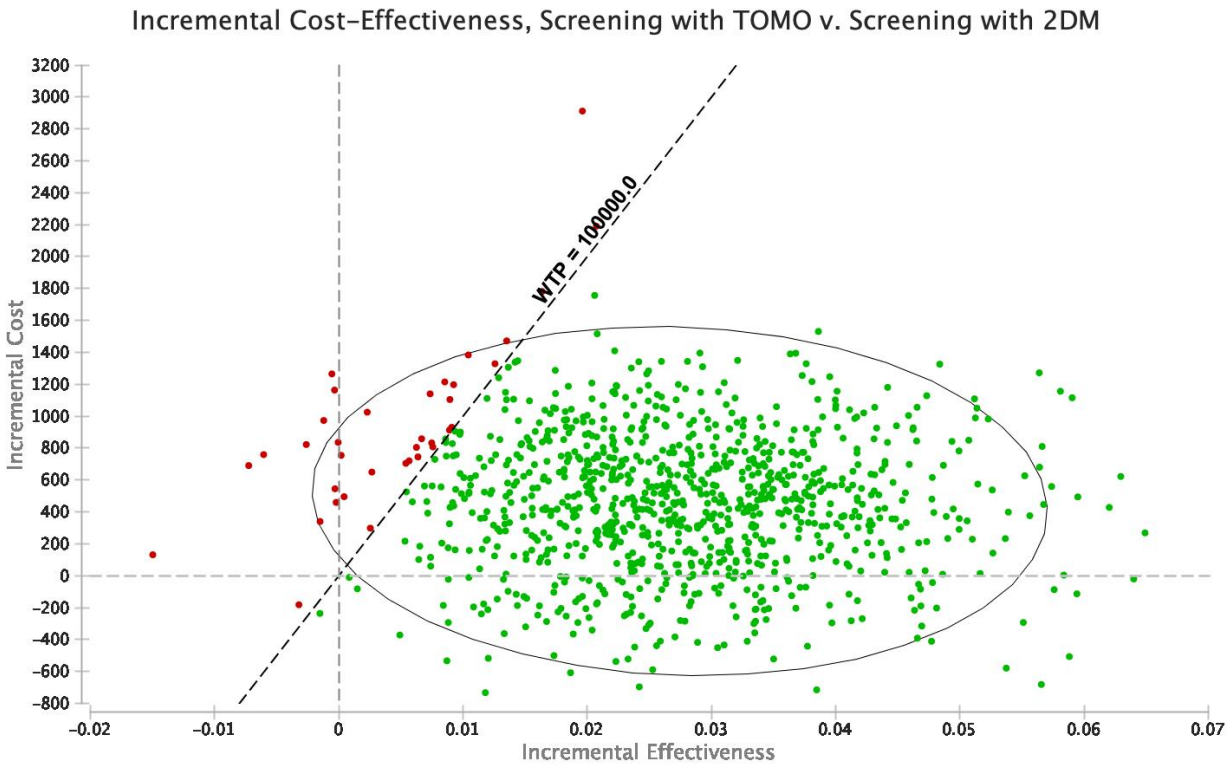

Figure S.3 Scatterplot of 100, 000 probabilistic scenarios from the Monte Carlo simulation

Table S.7 Base-case scenario results and deterministic analysis

Scenario	Description and supporting studies	Incremental costs	Incremental benefits (QALY)[1]	Incremental cost-effectiveness ratio (2019 CAD/QALY)
Base-case scenario	DBT+DM reimbursement fees are an additional $44 over DM alone, provide an absolute recall rate reduction of 2.2% and increases low-risk CDR by 0.16%	$470	0.027	$17,149
Absolute recall rate reduction low for the index exam	Absolute recall rate reduction only 1.1% for DM+DBT; for index mammogram only (16)	$518	0.013	$38,994
Absolute recall rate reduction low for all screening exams	Absolute recall rate reduction only 1.1% for DM+DBT; index and all	$544	-0.000	DM alone dominates

	subsequent exams, biennial over 25 years (15)			
Lowest additional cost of adding DBT to DM	Lowest additional cost of DBT over DM ($15) with reference to an observational cost analysis (34)	$113	0.027	$4,132
Overdiagnosis increased	DBT +DM introduces 10% more low-risk breast cancer	$504	0.016	$32, 309
Highest additional cost of adding DBT to DM ($75)	Highest additional cost of DBT from 2018 US Medicare fee for adjunct DBT (24)	$851	0.027	$31,073
Maximum absolute recall rate reduction (7.5%) on index and all subsequent exams	Optimistic absolute recall rate 7.5% reduction index, assuming the best possible recall rate reduction (3)	$28	0.194	$144
Maximum absolute recall rate reduction on index exam only (7.5%)	Optimistic absolute recall rate 7.5% reduction index and subsequent	$200	0.106	$1,883
Overdiagnosis decreased	DBT +DM reduces low-risk breast cancer rates by 10%	$435	0.039	$11,086
Disutility attributed to abnormal exam results	Assume utility decreases to 0.74 for first year of ever-abnormal with reference to published studies on disutility from cancer screening (35)	$470	0.037	$12,677
High-risk treatment costs	2X increase for all high-risk costs	$397	0.027	$14,513
Worse disutility from treatment of low-risk breast cancer	Reduce utility to 0.63 for five years if disutility from curative treatment is underestimated (36)	$470	0.027	$17,682
Breast cancer mortality	Breast cancer mortality 20% higher in both intervention arm and comparator	$475	0.028	$16,923

[1]Abbreviations: QALY, Quality-adjusted life years; DBT, digital breast tomosynthesis; DM, digital mammography

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