The cost-effectiveness of adding tomosynthesis to mammography-based breast cancer screening

Running title: economic impact of breast cancer screening with tomosynthesis

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ABSTRACT

Background: Observational studies show that digital tomosynthesis (DBT) combined with digital mammography (DM) can reduce recall rates and increases breast cancer detection rates. The objective of this study was to examine the cost-effectiveness of DBT + DM versus DM alone in British Columbia and identify impactful parameters that can improve the efficiency of breast cancer screening.

Methods: We developed a decision analytic model that used real-world data from a cohort of screening participants in the BC Cancer Breast Screening Program. The model simulated lifetime costs and outcomes for breast cancer screening participants, aged 40-74 taking the universal healthcare payer's perspective. We analysed healthcare resource utilization rates, health state costs and incremental cost-effectiveness ratios (ICERS).

Results: We found that the ICER was highly sensitive to recall rate reductions and insensitive to detection rates, breast cancer treatment costs, and disutility from screening or treatment. If DBT+DM can reduce absolute recall rates by more than 2.1%, the intervention would deliver an average 0.027 additional QALYs at an additional cost of $470 (2019 CDN); giving an ICER of $17,149/QALY. At commonly referenced thresholds of acceptability, >90% of the probabilistic simulations favored the adoption of DBT+DM versus DM alone.

Interpretation: The addition of DBT + DM would be considered cost-effective owing to the low positive predictive value of screening with DM alone. This finding depends heavily on the ability of DBT+DM to reduce absolute recall rates. Recall rate reductions should be monitored closely if the technology is adopted.

Funding Source: BC Cancer Breast Screening

Introduction

Digital Breast Tomosynthesis (DBT) is an imaging technique that may improve the specificity and positive predictive value of breast cancer screening. The new technology provides multiple planar images per breast screened, thereby enhancing the ability to distinguish between malignant and benign characteristics on digital mammography (DM) screening exams. Observational studies have shown that using DBT as an adjunct to DM screening reduces the rate of recall exams (1-13) and increases cancer detection rates (2, 5, 6, 12, 14-17). Meta-analysis suggest that recall rate reductions vary widely with the highest reduction rates from North American trials (18). The combined use of DBT+DM for breast screening has already been adopted in regions in the U.S. with greater socioeconomic resources (19). The underlying hypothesis favoring adoption of adjunct DBT assumes that there would be a reduction in total screening costs associated with less diagnostic workup for false positives, and lower rates of overdiagnosed breast cancer that is not life threatening. There are, however, concerns that the extra time required for radiologists to interpret the numerous additional images and data storage requirements may introduce costs that outweigh any potential savings (20, 21). As screening programs perform high volumes of breast exams, the decision to supplement DM-based screening with DBT requires data-driven analyses of the total costs and all downstream outcomes involved.

Economic models simultaneously combine multiple cost and outcomes data to project the average lifetime impacts from new interventions. The modeling can use data inputs from the literature, published statistics or real-world data from a defined cohort of screening participants. The later approach is referred to as "cohort modeling" defined by intrinsic properties of the cohort and its prevalent risk factors. Cohort modeling is preferred for healthcare decisions that require accurate capture of systems-generated uncertainty, such as varying false positive rates, cancer detection rates or survival after treatment for breast cancer. Cohort models can also rapidly account for combined parameter uncertainty with a probabilistic analysis—a sensitivity analysis that is required to adequately inform health policy with economic models (22). If data inputs are used to simulate outcomes for a hypothetical cohort, the modeling involves computational methods known as microsimulation. At the heart of microsimulation is the ability to simulate individual lives, widespread screening behaviours and potential outcomes for large populations with heterogenous risks.

The U.S. National Cancer Institute's Cancer Information and Surveillance modelling Network (CISNET) has independently developed three microsimulation models to inform national breast cancer screening policy. The models use data from the Surveillance and Epidemiology and End Results program (SEER) cancer registry and screening data from the Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR) consortium in a hypothetical cohort of eligible women. Two studies have been published that use these models to estimate the

cost-effectiveness of adjunct DBT for breast screening in the U.S. (23, 24). These studies have offered information to support decisions about the population at risk, based on the natural history of breast cancer and risks such as age and breast density. The economic simulations done with the CISNET models concluded that depending on the cost of DBT and the way cancer outcomes are simulated, the results generated can vary extensively, indicating a need for further economic evidence. The purpose of our study aligns with the need for more knowledge on breast screening economics by modeling with a population-based cohort model, accounting for uncertainty in the model and providing insights into the most impactful parameters.

Methods

Model overview

We developed a cost-effectiveness model to simulate the long-term economic impact of supplementing DM with DBT. British Columbia (BC), is considering the adoption of DBT as an adjunct to the provincial DM-based breast-cancer screening program. The model was co-developed with research team members from BC Cancer Breast Screening and clinical staff, who participated in the design of the model, analysis of the input data and validation of the results. The model used data for new screening participants, between the ages of 40-74, starting from their initial, or index, screening exam. We assumed 100% return rates for biennial exams, over 23 years of their eligibility in order to apply maximum possible increase in costs and maximum transitions to less preferred health states (i.e. abnormal, high- or low-risk breast cancer). Datasets from the Breast Screening Program and the BC Cancer Registry were linked to estimate the risk of having a breast cancer diagnosis and the risk of death after diagnosis of breast cancer in women who have ever received a screening mammogram. Outcomes from ever-screened patients who developed breast cancer were used to estimate long-term mortality and treatment costs that could be expected for screening with DBT+DM versus DM alone, assuming that the intervention offered a 2.2% absolute reduction in recall rates, as reported in a recent meta-analysis of observational DBT screening studies in North America (18). The total costs and benefits were simulated from the universal healthcare system payer's perspective over a 40-year, life-time horizon. The isolated and combined parameter uncertainty was assessed with deterministic and probabilistic sensitivity analyses, respectively. The model was programmed with TreeAge Pro, version 2020.

Screening Outcomes

The screening outcomes were defined as follows: Recall rate was the proportion of mammograms classified as abnormal according to the radiologist's interpretation. The cancer rate (CR) was the number of participants with cancer diagnosed within one year of a mammogram, per 1000 screens. The cancer detection rates (CDR) was the number of

participants with a cancer diagnosis within 12 months of an abnormal screen, per 1000 screens. The interval cancer rate (ICR) was the number of participants with a confirmed incident cancer within 0-12 months of their last screening exam which was negative, per 1000 screens. All screening outcome measures were defined for screening participants who had their baseline exam prior to December 31, 2015, allowing for at least a year of follow-up for comparison with the measures reported in other screening studies.

Cost-effectiveness modelling

The cumulative sum of all additional costs and benefits attributed to the adoption of DBT+DM versus DM alone was determined with the baseline assumptions that DBT+DM screening exams cost an additional $44 CDN over DM, offer an absolute 2.2% recall rate reduction and the CDR increased by 1.6 per 1,000 scans (18). For time-dependent transitions, the shape and slope parameters from Weibull regression were used to determine the transition probabilities. A full description of the cost and outcomes data inputs may be found in the supplementary material. All future costs and benefits were discounted to net present value at a rate of 3% per year. A series of screening scenarios were evaluated deterministically to define isolated parameter uncertainty from known or suspected sources including: absolute recall rate reductions, cancer detection rates, disutility for adverse quality of life associated with abnormal exam results, overdiagnosis of breast cancer that is not life threatening, and any potential stage shift from high-risk to low-risk breast cancer that would reduce complications through early detection and other individual assumptions throughout the model. A Probabilistic Sensitivity Analysis (PSA) was performed to test the combined parameter uncertainty in the model and the range of possible ICER estimates (supplementary methods). A standard threshold for acceptability of $100,000 per QALY was selected with reference to the thresholds used to evaluate cost-effectiveness with the CISNET models. The percentage of simulated ICERs that fell below this threshold was reported to account for overall combined parameter uncertainty.

Statistical Analysis

Chi-squared tests were used to detect differences in rates of histological subgroups between high and low-risk breast cancer and Mann-Whitney rank sum tests were used for differences in mean costs for breast cancer treatment across low- and high-risk subgroups, differences between means in the cohort data and mean follow-up time for low- versus high-risk breast cancer cost data. The odds ratio of a cancer diagnosis or subsequent abnormal exam was estimated using a multivariable logistic regression model that adjusted for age and the baseline exam result. All tests of statistical significance report a P value from two-sided tests, with a 5% threshold.

Ethics Approval

The study was approved by the University of British Columbia's Research Ethics Board.

RESULTS

There were 112 249 participants in the screening cohort with index mammograms recorded over the observation period. Their baseline demographic characteristics are provided in Table 1. The mean age for the onset of screening with the index exam is 49.3 years, and the majority of people in the cohort had their first exam between age 40-49. The average recall rate was higher for index exams versus all subsequent exams (19.5%, versus 9.0%) and the chances of having a subsequent abnormal exam was higher after an abnormal versus normal index exam (OR=1.24, 95%CI: 1.14 - 1.35). Of the 88 975 screening participants with at least one year of follow-up, 592 had breast cancer detected within one year of an abnormal index exam. The CDR was 6.7 per 1000 for index exams, and 1.7 per 1000 for all subsequent exams. There were 50 interval cancers that developed after a normal index screen, and the one-year ICR for index exams was 0.57 per 1000 and 0.12 per 1000 for subsequent exams. Of the cancers detected within one year of an abnormal exam, 373 (63%) were low-risk; while only 15 of the 50 interval cancers (30%) were low-risk.

The modelling parameters and assumptions are provided in Table 2. The treatment cost analysis used data from 809 patients in the screening cohort who developed breast cancer within the observation period and had lower proportions of hormone receptor positive breast cancer and younger age at diagnosis than the breast cancer cohort, but similar histology and stage characteristics. The difference is attributed to risks from age and/or menopausal status that distinguish new screening participants from all other breast cancer patients with screening exposure. The resource utilization rates and cost inputs shown in Table 3 indicate similar follow-up for patients in high-versus low-risk groups, over each of the five years analysed for costs thus rendering five years of resource utilization data available for analysis (all $p>0.1$). Total, five-year costs were significantly higher for high- versus low-risk breast cancer ($p<0.005$), due to the high cost of systemic therapy in the first year of breast cancer treatment (Figure 1).

The model predicts that the addition of DBT to DM screening would results in an additional 0.027 QALY, with an average incremental cost difference of $470 per-person (Table 4). The estimated incremental cost-effectiveness ratio is $17,149/QALY. The deterministic analysis showed that the most impactful parameters in the model were the absolute recall rate reductions; when this parameter was varied over the range of results reported in observational studies, either the intervention or the comparator would appear cost-effective. Increasing the costs to treat high-risk breast cancer, and cancer detection rates had only marginal impacts on the overall cost-effectiveness, due to the low number of individuals who receive a breast cancer diagnosis relative to the high number that are screened. The probabilistic sensitivity analysis showed that 98% of 100,000 iterations simulated fell below the commonly referenced willingness to pay

threshold of $100,000 per QALY (see supplementary materials). If DBT+DM reduces absolute recall rates by at least 2.1%, and the additional cost of providing DBT exams are not higher than the established reimbursement fees, the technology is likely to be considered a cost-effective addition to DM screening.

DISCUSSION

The cost-effectiveness adding DBT to DM screening depends critically on the ability of DBT to improve the specificity of DM—a screening intervention with low positive predictive values and high rates of overdiagnosis. Our analysis was most sensitive to parameters related to abnormal screening exam results and relatively insensitive to parameters related to cancer detection; specifically, there was negligible impact from breast cancer mortalities, higher treatment costs or disutility from overdiagnosis of low-risk breast cancer on their own. Using assumptions based on the existing literature, we find that the average incremental benefits provided by DBT+DM are small (0.027 QALYs per person), driven by DBT+DM enabling a lower probability of transitions to the ever-abnormal health state, and this benefit is achieved with an incremental cost of $470 per person.

Our findings add to the existing knowledge offered by CISNET microsimulation models though the identification of recall rates as the most impactful parameter. The main difference between our modelling approach and that of the CISNET microsimulation models come from distinction of an "ever-abnormal" health state. The strong economic effects of recall rate reductions may be washed out if the history of an abnormal exam is not accounted for as an independent risk factor. The majority of breast cancer screening participants can expect to receive an abnormal screen if they participate long enough with the current DM technology (25). Parameterizing recall rates independently also reflects the knowledge of a higher risk of developing breast cancer after having had an abnormal exam (26). There may also be subtle differences attributed to our use of data from breast cancer patients who had screening exposure, rather than using whole registry data for all breast cancer patients, regardless of screening history. Members of our research group have found that breast cancer outcomes are better for screening mammography participants compared to those not exposed to screening, and the treatments received by ever-screened participants were less intensive (27).

Recall rate reductions vary widely in observational DBT studies. Early population-based studies suggest that DBT+DM will be able to replicate observational findings (28). Definitive outcomes from the ongoing randomized Tomosynthesis Mammographic Imaging Screening Trial (TMIST) (NCT02616432), will, however clarify the diagnostic accuracy of DBT screening and its use to improve the stage distribution of screen-detected breast cancer. Central to these results will be

the ability of DBT + DM to reduce interval cancer rates, which are more likely to be diagnosed as high-risk breast cancer.

Limitations: Our study used data available for screening participants between age 40-74, and who use either a fixed location mammography clinic or mobile breast screening vans that service British Columbia. Breast density assessment was not adopted as routine screening practice in British Columbia until 2017; therefore, our analysis did not adjust for this variable. Our study is limited by the amount of follow-up available for simulating long-term breast cancer outcomes for screening participants. The screening literature in general is limited by the absence of patient-level data on disutility from abnormal exam results and/or low-risk breast cancer that may not have affected mortality if left untreated. There is an emerging literature on disutility for cancer screening that cite methodological challenges related to accurately obtaining this information from screening participants (29). These data therefore may not be visible in standard economic evaluations, such as those by CISNET and ours, that rely on standard health utility instruments.

Conclusion: If DBT can reduce recall rates and does not introduce additional screening costs, it is likely to be considered cost-effective. Improving the positive predictive value of breast cancer screening has the potential to improve program efficiency and there are several tools on the technology development horizon that aim to do so (30).

Data sharing statement: Data for this study are available as aggregated modelling parameters upon request

Role of the funder

The funder manages the provincial breast screening budget in British Columbia

Conflicts of interest

The authors declare no conflicts of interest

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Table 1. Baseline demographics and screening exam results

Dataset	Screening data
Number of index exams in the study cohort	112 249
Mean age at index exam (range)	49.3 (40-74)
40-49	68, 703 (61.2%)
50-59	27,976 (24.9%)
60-69	13, 688 (12.2%)
70-75	1, 902 (1.7%)
Ethnicity[1]	
European/British ancestry	56,706 (50.5%)
East/South East Asian	27, 614 (24.6%)
South Asian	7, 783 (6.9%)
Aboriginal peoples	2, 867 (2.5%)
West Asian	2, 130 (1.9%)
All others (including multiple ethnicities)	10, 848 (9.7%)
Not reported or unknown	7, 319 (6.5%)
Breast density (at index exam)	
A	10, 057 (9.0%)
B	24, 547 (21.9%)
C	27, 977 (24.9%)
D	9, 000 (8.0%)
Missing	40, 668 (36.2%)
Index exam year	
2012	9, 279 (8.3%)
2013	13, 558 (12.1%)
2014	19, 473 (17.4%)
2015	21, 869 (19.5%)
2016	23, 979 (21.4%)
2017	24, 091 (21.5%)
Recall rate	
Index exam abnormal/ total index exams (% total index exams)	21, 894/ 112, 249 (19.5%)
Subsequent abnormal exams / total subsequent exams (% of all subsequent)	4, 965/ 55, 304 (9.0%)
Completion rate	
Index exam (% total)	112, 249 (100.0%)
First subsequent (% total)	40, 019 (35.7%)
Second subsequent (% total)	11, 508 (10.3%)
Third subsequent (% total)	3, 037 (2.7%)
Fourth subsequent (% total)	632 (0.6%)
Fifth subsequent (% total)	108 (0.1%)

[1]all self-reported responses to race/ethnicity questions upon registration with BC Cancer Breast Screening totalling more than 1.0% for any subgroup, were included.

Table 2. Model parameters and assumptions

Parameter	Description	Source data and assumptions
Breast cancer screening and diagnosis		
Screening utilization rates	Biennial screening exams for new screening participants, assuming 100% return rates over 25 years	Maximum additional costs and the average age of new mammography screening participants
Abnormal index exam rate	Percentage of index mammograms identified as abnormal; 19.5% of all index exams	Screening cohort, index exam
Subsequent abnormal exam rate	Probability of a subsequent abnormal exam; 9.0%	Screening cohort, subsequent exams
Detection after an abnormal exam	Time-dependent rate of developing breast cancer following history of any abnormal exam result	Screening cohort linked with breast cancer cohort
Incremental cancer detection rate	Additional incidences of low-risk breast cancer applied to the intervention arm attributed to increased CDR from DBT+DM over DM alone (an additional 1.6 per 1000), applied biennially over 25 years	Parameter assumption based on meta-analysis (18)
Undetected breast cancer	Time-dependent rate of developing breast cancer in the absence of any abnormal exam result, by high- or low-risk breast cancer	Screening cohort linked with Breast cancer cohort
Absolute recall rate reduction	Absolute recall rate reduction from meta-analysis of observational trials for the use of DBT versus DM (2.2%), applied biennially over 25 years	Parameter assumption based on meta-analysis (18)
Mortality		
Survival	Long-term survival for ever-screened participants, after diagnosis, by high- or low-risk breast cancer	Breast cancer cohort
Background mortality	Age- and Sex- specific mortality adjustments by five-year age groupings	Statistics Canada data for female mortality by age, in BC
Costs		
Screening	$125 for digital mammography; $169 for combined digital mammography and tomosynthesis, applied biennially, over 25 years	Established billing fees for Alberta Health Services[1]
Diagnostic evaluation	$550 following the first abnormal exam	Mean cost for investigation in BC[1]
Treatment costs	Health state-specific costs, in 2019 CDN dollars	Resource utilization rates and unit costs for screening participants who had breast cancer
Utilities		
Screening with normal exam results	Quality of life expected for screening with normal exam results, 0.006 decrease in utility score for one week after having a mammogram (0.994)	Matched CISNET assumption[2]
Screening with an abnormal exam result	Quality of life following an abnormal exam result. Year 1, utility=0.990 (5 weeks of disutility); Years 2-40 returns to 1.000	CISNET assumptions for false positive exams[2]
Low-risk breast cancer	Utility weight of 0.900 for two years, then returns to 1.000	CISNET assumptions for localized breast cancer and expert opinion[2]
High-risk breast cancer	Utility weight of 0.750 for the first 13 years, then 0.600 for years 14-40.	CISNET assumptions for advanced breast cancer and expert opinion[2]

[1]Unit costing described in full detail in the supplementary materials

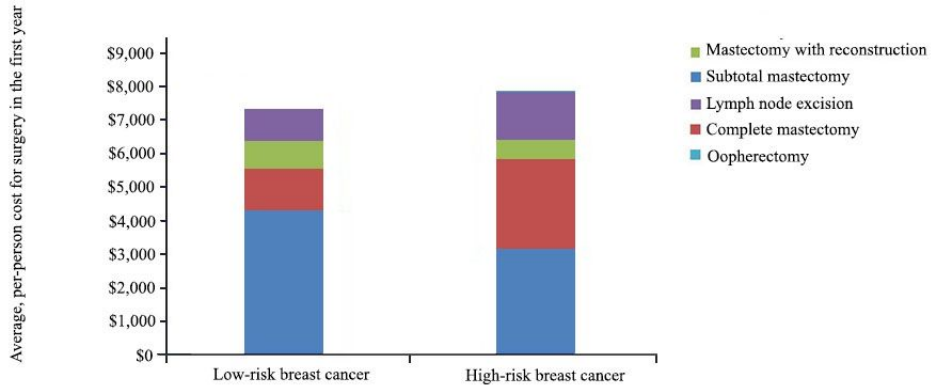
[2]Common model inputs used by the CISNET modeling group (33)

Table 3. Resource utilization rates and costs for breast cancer treatment

Health state	Year	Resource	Resource utilization rate (per person)	Mean cost (95%CI)
Low-risk breast cancer	1	Surgery	1.00	$7,312 ($7,111-$7,512)
		OncotypeDx	0.51	$2,719 ($2,480-$2,957)
		Systemic therapy	0.59	$3,008 ($2,085-3,931)
		Radiotherapy	0.51	$4,283 ($3,893-$4,667)
		End of life breast cancer care	n.r.[1]	$0.00
	2	Surgery	n.r.	$85 ($17-$153)
		Systemic therapy	0.53	$1,577 ($999-$2,156)
		Radiotherapy	0	$54 ($-22-$131)
		End of life breast cancer care	n.r.	$0.00
	3	Surgery	0.06	$40 (-$16-$96)
		Systemic therapy	0.48	$450 ($123-$776)
		Radiotherapy	n.r.	$90 ($-50-$231)
		End of life breast cancer care	n.r.	$0.00
	4	Surgery	0	$213 (-$206-$634)
		Systemic therapy	0.5	$241 ($137-$346)
		Radiotherapy	0.01	$120 ($-50-$288)
		End of life breast cancer care	n.r.	$214 ($-106-$634)
	5	Surgery	0	$79 (-$77-$235)
		Systemic therapy	0.48	$516 (-$251-$1,285)
		Radiotherapy	0	$0.00
		End of life breast cancer care	n.r.	$0.00
	6-40	Continue year 5		
High-risk breast cancer	1	Surgery	0.96	$7,881 ($7,547-$8,216)
		Systemic therapy	0.98	$19,664 ($17,496-$21,832)
		Radiotherapy	0.79	$9,019 ($8,457-$9,581)
		End of life breast cancer care	n.r.	$274 ($-106-$655)
	2	Surgery	0.02	$111 ($10-$213)
		Systemic therapy	0.83	$ 7,718 ($5,736-$9,699)
		Radiotherapy	n.r.	$285 ($102-$468)
		End of life breast cancer care	n.r.	$277 ($-107-$621)
	3	Surgery	0	$0.00
		Systemic therapy	0.76	$ 4,004 ($1,967-$6,312)
		Radiotherapy	n.r.	$106 ($0-$212)
		End of life breast cancer care	n.r.	$960 ($124-$1,795)
	4	Surgery	0	$0.00
		Systemic therapy	0.7	$1,574 ($404-$2,743)
		Radiotherapy	0.01	$112 (-$14-$237)
		End of life breast cancer care	n.r.	$984 (-$124-$2,095)
	5	Surgery	0	$0.00
		Systemic therapy	0.7	$ 1,619 (-$76-$3,314)
		Radiotherapy	0	$0.00
		End of life breast cancer care	n.r.	$647 (-$630-$1,925)
	6-40	Continue year 5		

[1]n.r.= not reportable, results for fewer than 10 individuals are not reported

A)


Average, per-person cost for surgery in the first year
$9,000
$8,000
$7,000
$6,000
$5,000
$4,000
$3,000
$2,000
$1,000
$0
Low-risk breast cancer
High-risk breast cancer
Mastectomy with reconstruction
Subtotal mastectomy
Lymph node excision
Complete mastectomy
Oopherectomy

B)

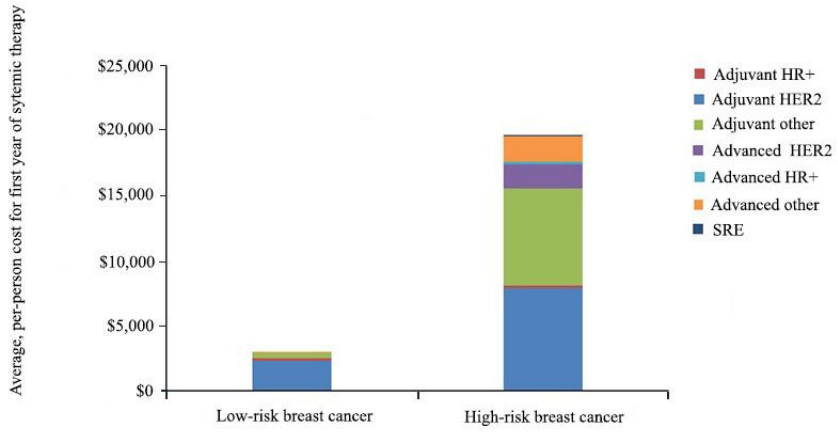

Average, per-person cost for first year of sytemic therapy
$25,000
$20,000
$15,000
$10,000
$5,000
$0
Low-risk breast cancer
High-risk breast cancer
Adjuvant HR+
Adjuvant HER2
Adjuvant other
Advanced HER2
Advanced HR+
Advanced other
SRE

Table 4. Base-case 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 subsequent exams, biennial over 25 years (15)	$544	0.000	DM alone dominates
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
Breast cancer mortality	Breast cancer mortality 20% higher	$475	0.028	$16,923
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

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

Supplementary material

S1. Cost and outcomes data

a) Screening outcomes

A subcohort was defined for 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. Linkage between the screening database and the BC Cancer Registry was performed using each participant's unique personal health number for calculation of breast cancer incidences, screening outcome measures and for evaluating the time-dependent probability of developing breast cancer after screening.

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

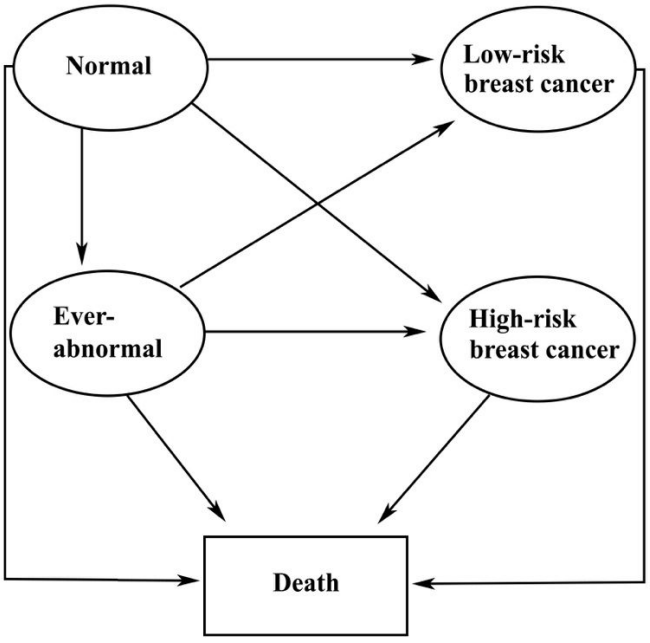


Figure S.1 Health states and transitions in the model

S. 2. Transition probabilities

In the development of the model, the study team found it necessary to make the distinction between "normal" and "ever-abnormal" screening health states due to anticipated differences in healthcare costs, health utility (or quality of life) and breast cancer incidence rates. The rationale for dividing breast cancer into "low-" and "high-risk" health states relate to the available therapies and prognostic risk. At any point after the index mammogram, screening participants may shift to another health state along a permitted path, including transition from "normal" to "ever-abnormal", but not the reverse direction, since the risk of cancer in women who received an abnormal is higher OR: 16.08 (95%CI:13.56-19.06), as is the risk of a future abnormal exam (OR=1.24, 95%CI: 1.14 – 1.35).

Transitions from normal or ever-abnormal to low- or high-risk breast cancer, or death 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. A half-cycle correction was applied to the first and final years simulated with the model. This standard method is applied to account for mid-cycle membership that tends to be under- or over-estimated in the first and final cycles of the Markov process, respectively (37). Age-related background mortality rates were added to the observed rate of breast cancer deaths in the study cohort using national life tables from Statistics Canada, for women in the province of British Columbia. Utility assumptions were made to match to the CISNET models when possible, and expert opinion at BC Cancer otherwise (24).

Table S.2 Transition probabilities and distributions

Parameter	Comparison arm	Initial value	Weibull parameters	Distribution parameters reference
Normal index	DBT+DM	0.8260	n/a	95% CI from meta-analysis[1]

mammogram (initial)	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%)
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
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	
Unilateral subcutaneous mastectomy with implant prosthesis (9721)	Hospital facility and admin costs	$8,287.79	Case costing for breast cancer surgery, 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	
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]
	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]
	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 distribution parameters were set to the mean and standard error of the data, or the 95% confidence intervals reported for data from the published literature

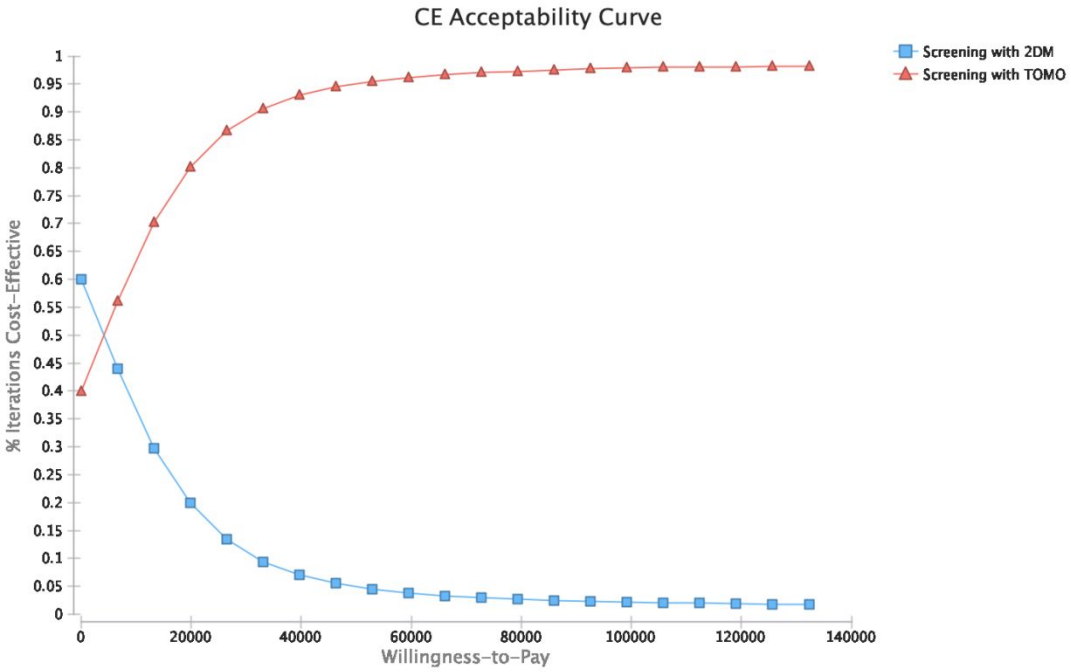


Figure S.2. Cost-Effectiveness Acceptability Curve from the Probabilistic Sensitivity Analysis comprised of 100, 000 iterations of Monte Carlo simulations with simultaneous sampling of all parameter distributions