2017

REPORT

A SINGLE-TECHNOLOGY ASSESSMENT

Digital Breast Tomosynthesis with Hologic 3D mammograhy Selenia Dimensions System for use in breast cancer screening

Norwegian Institute of Public Health

Title	Digital Breast Tomosynthesis with Hologic 3D mammograhy Selenia Dimensions System for use in breast cancer screening. Single-technology assessment
Norwegian title	Digital Brysttomosyntese med Hologic 3D mammograf Selenia Dimensions System i screening for brystkreft. Hurtigmetodevurdering.
Institution	Norwegian Institute of Public Health (Folkehelseinstitutttet) Camilla Stoltenberg, *Director*
Authors	Movik, Espen *Health Economist (project coordinator)* Dalsbø, Therese Kristine, *Senior Adviser* Fagelund, Beate Charlotte, *Health Economist* Friberg, Eva Godske, *Scientific Director, Norwegian Radiation Protection Authority* Håheim, Lise Lund, *Senior Researcher* Skår, Åse, *Senior Adviser*
ISBN	978-82-8082-873-6
Type of report	A single technology assessment (Hurtig metodevurdering)
No. of pages	70, (80 including appendices)
Client	The Ordering Forum (Bestillerforum RHF)
Subject heading (MeSH)	Breast Neoplasms; Mammography; Imaging, Three-Dimensional; Mass Screening; Radiation Dosage; Cost-Effectivenesst Analysis; Technology Assessment, Biomedical
Citation	Movik E, Dalsbø TK, Fagerlund BC, Friberg EG, Håheim LL, Skår Å Digital Breast Tomosynthesis with Hologic 3D mammography Selenia Dimensions System for use in breast cancer screening. A single technology assessment from Norwegian Institute of Public Health (Folkehelseinstitutttet). Oslo: Norwegian Institute of Public Health, 2017.

Norwegian Institute of Public Health
Oslo, September 2017

Sammendrag

Bakgrunn

Det offentlig finansierte Mammografiprogrammet tilbyr screening for brystkreft med røntgenundersøkelser av brystene hvert annet år til kvinner 50-69 år i Norge. Hensikten er å redusere dødeligheten av brystkreft ved å oppdage svulstene på et tidligere stadium. Screeningteknologien som brukes, digital mammografi (DM), innebærer å ta to todimensjonale (2D) røntgenbilder av hvert bryst fra forskjellige vinkler. En av begrensningene med denne teknologien er at små svulster kan være skjult bak vanlig brystkjertelvev, og vanskelig å oppdage, særlig i tette bryst. Digital brysttomosyntese (DBT) kombinert med DM kan redusere dette problemet ved å gi en tredimensjonal (3D) modell av brystet, på grunnlag av en serie med 2D bilder. Teknologien gjør det også mulig å konstruere "syntetiske" 2D bilder (S2D) tilsvarende standard digitale mammografibilder. En kombinasjon av disse systemene kan øke evnen til å oppdage svulster i brystet, og redusere behovet for at kvinner blir innkalt til etterundersøkelser for å bekrefte eller avkrefte om det er kreftsvulst i brystet. Det kan imidlertid også førte til at screeningundersøkelsen avdekker flere svulster som ubehandlet ikke ville ha påvirket kvinnens liv eller helse, altså økt overdiagnostikk. Når vi skal vurdere nye metoder for brystkreftscreening bør vi også ta hensyn til i hvilken grad undersøkelsene utsetter kvinnene for røntgenstråling.

Bestillerforum ga Kunnskapssenteret i Folkehelseinstituttet i oppdrag å utarbeide en hurtigmetodevurdering om "*Tredimensjonal digital brysttomosyntese (DBT) i screening for brystkreft"* (ID2015_041) 25. januar 2016. En hurtigmetodevurdering er en kunnskapsoppsummering med fokus på effekt, sikkerhet og kostnadseffektivitet.

Formål

Formålet med denne hurtigmetodevurderingen er å vurdere effekt, sikkerhet og kostnadseffektivitet ved digital brysttomosyntese i screening for brystkreft i Norge.

Det finnes flere produsenter av DBT-systemer, men bare Hologic Inc. har hittil (juni 2017) sendt inn en dokumentasjonspakke. Vi har utført en hurtigmetodevurdering om bruk av Hologic Selenia Dimensions digitale mammografisystem for brystkreftscreening, basert på den innsendte dokumentasjonspakken. Denne hurtigmetodevurderingen dekker ikke bruk av DBT i diagnostikk av brystkreft i klinisk praksis.

Evaluering av dokumentasjonen

Klinisk effekt

Dokumentasjonen som selskapet sendte inn besto av 12 studier identifisert ved et systematisk litteratursøk. Vi inkluderte fire publikasjoner som oppfylte våre inklusjonskriterier i denne hurtigmetodevurderingen.

Vi vurderte den foreliggende dokumentasjon ved hjelp av en forhåndsdefinert PICOS (Population, Intervensjon, Comparator, Outcomes og Study design), data om vurdering av risiko for systematiske feil, dataekstraksjon, og gradering av tilliten til resultatene ved hjelp av GRADE vurdering (The Grades of Recommendation, Assessment, Development and Evaluation). Vi har også gjennomgått analysene av kostnadseffektivitet og budsjettkonsekvenser som er beskrevet i dokumentasjonspakken.

Stråledose og risikovurdering

Produsenten ga ingen dokumentasjon om risiko forbundet med stråledosen med DBT. Vi har derfor gjennomført en egen vurdering av risikoen som er knyttet til strålingen som kvinner blir utsatt for ved bruk av DBT.

Kostnadseffektivitet

Hologic sendte inn en helseøkonomisk analyse basert på en amerikansk modell for analyse av diskrete hendelser, som de brukte for å beregne vunnede kvalitetsjusterte leveår. Hologic sammenlignet effekten av DBT + DM (S2D) for en hypotetisk kohort av kvinner som ble fulgt gjennom ti runder med screening over en 20-års tidshorisont. Modellen var basert på data (sensitivitet og spesifisitet) fra en foreløpig analyse av Oslo Tomosynthesis Screening Trial. Hologic hadde ikke tilgang til modellen, og gjennomførte kostnadsberegningene separat. De viktigste kostnadskomponentene var kostnader ved screeningen og kostnader ved behandling av brystkreft brutt ned på sykdomsstadier. Kostnadene ble anvendt på modellresultatene og variert i en rekke enveis sensitivitetsanalyser.

Resultater

Klinisk effekt

Vi har vurdert Hologic digital bryst tomosyntese i kombinasjon med standard digital mammografi eller syntetisk digital mammografi sammenliknet med digital mammografi alene. Fordi resultatene bare bygger på observasjonsstudier, har vi i utgangspunktet liten tillit til dem, vurdert ut fra GRADE. For enkelte av resultatene har vi gradert tilliten ned ytterligere.

De viktigste funnene er:

- Vi er usikre på om andelen kvinner som blir innkalt til etterundersøkelse reduseres eller økes (svært lav tillit pga. motstridende funn i studiene).
- Andelen brystkreft oppdaget ved sceening kan øke (lav tillit til resultatene).
- Vi er usikre på om andelen kvinner som får påvist intervallkreft påvirkes (svært lav tillit til resultatene pga. lite dokumentasjon).
- Vi er usikre på om andelen kvinner med falske positive funn reduseres eller økes (svært lav tillit pga. motstridende funn i studiene).
- Sensitiviteten er muligens uendret, men spesifisiteten kan muligens øke (lav tillit til resultatene)
- Vi er usikre på om andelen kvinner med falske negative funn reduseres eller økes (svært lav tillit pga. lite dokumentasjon).
- Studiene rapporterte ingen informasjon om dødelighet og livskvalitet

Lav tillit til resultatene betyr at ny forskning kan endre resultatene og våre konklusjoner.

Stråledose og risikovurdering

For alle screeningmodellene som er vurdert vil bruk av Hologic Selenia Dimensions DBT-system i Mammografiprogrammet føre til at kvinnene blir utsatt for en økt stråledose og derved også økt risiko for stråleindusert kreft sammenlignet med dagens praksis med digital mammografi.

Sammendrag av funn basert på doser rapportert i OTST og STORM-2-studiene:

- DBT alene: Dosen og risikoen vil øke med 23 % til 38 %, noe som resulterer i en total absorbert dose til granulært vev (AGD) på 3,7-3,9 mGy og en estimert forekomst av stråleindusert brystkreft på 15 til 16 per 100 000 kvinner og dødelighet på 1,2 per 100 000 kvinner.
- DBT + DM: Dosen og risikoen øker med en faktor mellom 2,23 og 2,37, noe som resulterer i en total AGD på 6,4-7,0 mGy og en estimert forekomst av stråleindusert brystkreft på 26 til 29 per 100.000 kvinner og dødelighet på 2,1 til 2,3 per 100.000 kvinner.
- DBT + S2D: Dosen og risikoen økes med 23 % til 38 %, men reduseres med 42 % til 45 % sammenlignet med DBT + DM, noe som resulterer i samme dose og risiko som DBT alene.

De estimerte verdiene for forekomst av stråleindusert brystkreft og dødelighet må tolkes med forsiktighet, da det er høy grad av usikkerhet knyttet til dem. Imidlertid gir forholdet mellom doser og risiko for de forskjellige screeningmodeller gyldig informasjon til den samlede vurderingen av nytte og risiko som skal gjøres for screeningsprogrammet.

Kostnadseffektivitet

Normaltilfellet («base case») fra den innsendte økonomiske analysen av DBT + DM (S2D) vs. DM alene var 0,007 kvalitetsjusterte leveår (0,007 QALYs) vunnet per kvinne som blir screenet. Den inkrementelle kostnadseffektivitetsratioen (ICER) var ca. 144 000 NOK per vunnet QALY. Dette resultatet er beregnet for en befolkning av kvinner med tette bryst.

Hologic baserte analysen av budsjettkonsekvenser på tre komponenter: relative kostnader for innkjøp av utstyr, kostnader ved screening og kostnader ved behandling av brystkreft. Normaltilfellet («base case») var en nettoøkning på utgifter på 77,5 millioner kroner i år 5 etter innføring av DBT + DM (S2D). Hologic inkluderte også en sensitivitetsanalyse i budsjettkonsekvensanalysen for å fastslå effekten av å variere prisen, som ennå ikke er bestemt, av DBT-utstyret, og undersøke hvordan endringer i viktige forutsetninger ville påvirke resultatene. Sensitivitetsanalysene viste stor variasjon i netto økning i utgifter.

Diskusjon

Klinisk effect og sikkerhet

Sammenlignet med digital mammografi alene, kan bruk av Hologic digital bryst tomosyntese i kombinasjon med standard digital mammografi eller syntetisert digital mammografi øke andelen av brystkreft som avdekkes ved screening (kreftdeteksjonsrate eller CDR), ifølge alle studiene. Studiene har gitt dokumentasjon knyttet til den første screeningrunden ved bruk av DM + DBT, noe som delvis kunne forklare den betydelige økte kreftdeteksjonsraten sammenlignet med screening med DM alene. Vi må ha estimater for andelen kvinner med brystkreft som blir oppdaget ved gjentatt DBT-screening av de samme populasjonene for å kunne tallfeste effekten av å bruke DBT i tillegg til DM på både kreftdeteksjon og på andelen som har falske positive funn ved gjentatte screeningundersøkelser.

Randomiserte studier som undersøker effekten av å bruke DBT i tillegg til standard eller syntetisk DM sammenlignet med dagens praksis med DM alene på forekomst av intervallkreft som et surrogat utfall for fordelen ved screening, vil kunne gi nødvendig dokumentasjon for å understøtte fremtidig politikk og praksis når det gjelder brystkreftscreening i befolkningen. De randomiserte studiene bør utformes slik at de samtidig kan undersøke andre kunnskapshull, slik som hvordan det vil påvirke ulike mål for evnen til å påvise brystkreft ved gjentatt screening med DBT, og kostnadseffektiviteten ved bruk av DBT.

Bruk av både DBT og standard DM forårsaker en økning i stråledosen. DBT-systemer som kan generere syntetiske 2D-bilder er svært gunstige sammenlignet med

DBT i kombinasjon med full-felt digital mammografi (standard DM), fordi det gir lavere stråledose og tilhørende risiko. Informasjon om stråledoser bør inkluderes i fremtidige kliniske studier.

Kostnadseffektivitet

Den helseøkonomiske analysen som produsenten sendte inn tydet på at DBT i tillegg til DM sammenlignet med gjeldende screeningpraksis kan føre til tidligere påvisning av brystkreft og at en lavere andel kvinner innkalles til etterundersøkelse, men mulig reduserte kostnader som følge av færre etterundersøkelser var ikke modellert. Resultatene antydet derfor at DBT kan være kostnadseffektivt hvis det blir tatt i bruk i Mammografiprogrammet. Det er imidlertid en rekke forhold som bidrar til at resultatene er usikre. For det første er den kliniske effekten usikker, spesielt med hensyn til sensitivitet, over gjentatte screeningundersøkelser og på tvers av ulike populasjoner (for eksempel med hensyn til brysttetthet). For det andre vet vi ikke i hvilken grad den mulige økningen i evnen til å oppdage brystkreft kan føre til økt overdiagnostikk og unødvendig behandling. For det tredje, siden produsenten ikke kunne levere en sammenhengende og tilpasset helseøkonomisk modell, er det vanskelig å fastslå konsekvensene av ulike antagelser i analysen samt vurdere den samlede usikkerheten som er knyttet til de helseøkonomiske resultatene.

Konklusjon

Vi mangler dokumentasjon for å konkludere om effekten av å bruke Hologic digital bryst tomosyntese kombinert med digital mammografi eller syntetisert digital mammografi sammenlignet med digital mammografi alene for de utfallene som vi har vurdert (andel etterundersøkelser, andel av brystkreft oppdaget ved screening, andel brystkreft påvist utenom screening (intervallkreft), andelen kvinner med falske positive og falske negative funn, sensitivitet, spesifisitet, dødelighet og livskvalitet).

Når det foreligger tilstrekkelig dokumentasjon bør det vurderes om det skal utarbeides en fullstendig metodevurdering.

Executive summary

Background

In Norway, breast cancer screening is offered through a publicly funded program to women in the age group 50-69 on a biennial basis. Breast cancer incidence is relatively higher among women in this age group than it is among younger women. The purpose of the screening program is to reduce breast cancer-related mortality by detecting tumors at an earlier stage. The screening technology in current use, known as digital mammography (DM), involves capturing two two-dimensional images of each breast from different angles. One of the limitations of this technology is that tumors may be "masked", and difficult to detect, especially in dense breasts. Digital breast tomosynthesis (DBT) may, when employed in combination with DM, alleviate this problem by providing a 3D model of the breast constructed on the basis of a series of 2D images. The technology also involves an option to construct "synthetic" 2D images (S2D) similar to a standard digital mammogram. The combined systems have the potential to increase detection rates while reducing the need for patient recall to confirm or rule out the presence of a tumor. However, this means that additional tumors could be detected which do not require treatment during the patient's lifetime, thus increasing the rate of overdiagnosis. Mammography screening involves radiation exposure, a factor which has to be taken into account when new screening technologies are evaluated.

"Bestillerforum" requested the National Institute of Public Health to perform a single technology assessment (STA) regarding "*Three dimensional digital breast tomosynthesis in screening for breast cancer"* (ID2015_041) on January 25, 2016. An STA focuses on a clinical effectiveness and safety assessment along with a cost-effectiveness analysis of this single-technology (device).

Objective

The objective of this single technology assessment (STA) is to assess the efficacy, safety, and cost-effectiveness of digital breast tomosynthesis in breast cancer screening in Norway.

There are several manufacturers of DBT systems, but only Hologic Inc., has to date (June 2017) submitted a documentation pack. We have performed a single technology assessment of the use of Hologic Selenia Dimensions digital mammography system for breast cancer screening, based on the submission from Hologic Inc. We do not cover the use of the system in the diagnosis of breast cancer in clinical practiceby this STA.

Evaluation of the documentation

Clinical effectiveness

The documentation submitted by the company consisted of 12 studies identified by a systematic literature search. Four publications met our inclusion criteria and are included for assessment in this STA.

We have assessed the present documentation using a pre-defined PICOS (Population, Intervention, Comparator, Outcomes and Study design), risk of bias assessment of data provided by the submission file, data extraction, and graded the certainty of the evidence for the estimates using GRADE (The Grades of Recommendation, Assessment, Development and Evaluation) assessment. We have also reviewed the cost-effectiveness analysis and budget impact analysis described in the submission.

Radiation dose and risk assessment

The submitter provided no documentation assessing the risk associated with the radiation dose with DBT. Therefore, we conducted a separate assessment of the potential risks associated with radiation exposure with DBT.

Cost-effectiveness

Hologic submitted a health economic analysis based on an American discrete event analysis model, from which they had drawn results in terms of quality-adjusted life years gained. Hologic compared the effects of DBT+DM (synthetic 2D) for a hypothetical cohort of women that was followed through 10 rounds of screening over a 20-year time horizon. The model was based on data (sensitivity and specificity) from an interim analysis of the Oslo Tomosynthesis Screening Trial. Hologic did not have access to the model, and carried out the costing calculations separately. The main cost components were screening costs and breast cancer treatment costs broken down by disease stage. Costs were applied to the model results and varied in a number of one-way sensitivity analyses.

Results

Clinical effectiveness

Our main findings are as follows:

- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthezised digital mammography decreases or increases **recall rates** compared to digital mammography alone (very low confidence due to conflicting evidence from observational studies)
- The intervention may increase the rate of **screening-detected cancer** (cancer detection rate (CDR) according to all studies (very low confidence due to sparse evidence from one observational study).
- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthezised digital mammography makes any difference with regard to the detection of **interval cancer** compared to digital mammography alone (very low confidence in the evidence due to sparse evidence from one observational study).
- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthezised digital mammography decreases or increases **false positive rates** compared to digital mammography alone (very low confidence due to conflicting evidence from observational studies).
- The intervention may provide similar **sensitivity** rates, but may increase **specificity** rates (low confidence due to evidence from observational studies)
- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthezised digital mammography decreases or increases **false negative rates** compared to digital mammography alone (very low confidence due to sparse evidence from one observational study).
- Information on **death** and **quality of life** was not reported.

Uncertainty regarding the effect estimates means that new research may alter the results and our conclusion.

Radiation dose and risk assessment

When compared to the current practice with DM, introducing the Hologic Selenia Dimensions DBT-system into the Norwegian Breast Cancer Screening Programme (NBCSP) will result in an increased radiation dose followed by an increased risk of radiation-induced cancer for all the evaluated interventions defined by the PICO.

Summary of findings based on doses reported in the OTST and STORM-2 trial:

- DBT only: The dose and risk will increase by 23% to 38%, resulting in a total absorbed dose to granular tissue (AGD) of 3.7-3.9 mGy and an estimated incidence of radiation-induced breast cancer of 15 to 16 per 100,000 women and mortality of 1.2 per 100,000 women.

- DBT + DM: The dose and risk will increase by a factor of between 2.23 and 2.37, resulting in a total AGD of 6.4-7.0 mGy and an estimated incidence of radiation-induced breast cancer of 26 to 29 per 100,000 women and mortality of 2.1 to 2.3 per 100,000 women .
- DBT + S2D: The dose and risk will be increased by 23% to 38%, but reduced by 42% to 45% compared to DBT + DM, resulting in the same dose and risk as DBT alone.

The estimated values for incidence of radiation-induced breast cancer and mortality must be interpreted with caution as there is a high level of uncertainty associated with them. However, the ratio between doses and risks for the different interventions provides valid input to the total risk-benefit evaluation to be done for the screening program.

Cost-effectiveness

The base case results of the submitted economic analysis of DBT+DM (S2D) vs. DM alone were 0,007 quality adjusted life years gained per woman screened. The incremental cost per QALY gained was approximately NOK 144 000. This result is estimated for a population of women with dense breasts.

Hologic based the budget impact analysis on three components: relative costs of equipment procurement, screening costs, and breast cancer treatment costs. The base case estimate was a net increase in expenditure of 77.5 million NOK in year 5 after implementation. Hologic also included sensitivity analysis in the budget impact analysis to determine the effect of varying the price, which has yet to be determined, of the DBT equipment, and to examine how changes in important assumptions would influence the results of the budget impact analysis. The net increase in expenditure reported varied significantly in the sensitivity analyses.

Discussion

Clinical efficacy and safety

Compared to digital mammography alone, the use of Hologic digital breast tomosynthesis in combination with standard digital mammography or synthesized digital mammography may increase the rate of screening-detected cancer (cancer detection rate or CDR) according to all studies. The studies have provided evidence on the first screening round using DM+DBT, which could partly account for the substantial increased cancer detection rate, compared with standard screening with DM alone. Estimates of cancer detection rates for repeated DBT screening of the same populations are needed to quantify the effect of adjunct DBT on both cancer detection and false positive recalls at repeated screening rounds.

RCTs assessing the impact of adjunct DBT on interval cancer rates as a surrogate for screening benefit would provide critical evidence to underpin future population screening policy and practice. RCTs should be designed to simultaneously address additional evidence gaps such as DBT's incremental cost–effectiveness, and detection measures at repeat screening with adjunct DBT.

Using both DBT and standard DM (dual acquisition) causes an increase in the radiation dose. DBT-systems with the possibility to generate synthetic 2D images is highly favourable compared to DBT in combination with full field digital mammography, due to its reduction in dose and associated risk. Information on radiation doses should be included in future clinical trials.

Cost-effectiveness

The results from the submitter's health economic analysis indicated that adjunct DBT compared to current screening practice could lead to earlier detection of breast cancer and a lower recall rate, though potential cost reductions resulting from the latter are not actually modelled. The results suggest therefore that adjunct DBT could be cost-effective if adopted by the Norwegian Breast Cancer Screening Programme. However, there are a number of issues that contribute to uncertainty regarding the results. First, the uncertainty described above with regard to the clinical effectiveness, particularly with regard to sensitivity, over repeated screening visits and across different populations (e.g. with respect to breast density). Second, we do not know to what extent the potential increase in breast cancer detection may lead to increased overdiagnosis and unnecessary treatment. Third, since a coherent, adapted health economic model could not be supplied, it is difficult to ascertain the impact of various assumptions in the analysis and assess the total uncertainty regarding the health economic results.

Conclusion

There is too little evidence to conclude regarding the effects of the use of Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography compared to digital mammography alone for the outcomes assessed in our report (recall rates, cancer detection rate, interval cancer rate, false positive and false negative rate, sensitivity, specificity, mortality and quality of life).

Preparation of a full health technology assessment should be considered when sufficient evidence is available.

Table of contents

SAMMENDRAG **2**
Bakgrunn 2
Formål 2
Evaluering av dokumentasjonen 3
Resultater 3
Diskusjon 5
Konklusjon 6

EXECUTIVE SUMMARY **7**
Background 7
Objective 7
Evaluation of the documentation 8
Results 9
Discussion 10
Conclusion 11

TABLE OF CONTENTS **12**

PREFACE **14**
What is a single-technology assessment 14
Objective 14
Log 14
Project group 15
List of abbreviations 16

BACKGROUND **17**
Name of the device and the manufacturer responsible for the submission 17
Current use 17
Description of the technology 18
Breast cancer epidemiology 19
Breast cancer screening 20
DM and DBT or DM alone in breast cancer screening 23
Earlier recommendations 24

CLINICAL EFFECTIVENESS **26**
The main research questions 26
Literature searches and identification of relevant published literature 27

Characteristics of included studies 30
Risk of bias in included studies 32
Results 33
Summary of findings – clinical effectiveness 35

RADIATION DOSE AND RISK ASSESSMENT 37
Justification of medical exposure – clinical benefits versus radiation detriments 37
Radiation doses 37
Radiation risk – induced breast cancer incidence and mortality 41
Summary of findings – radiation dose and risk assessment 44

COST-EFFECTIVENESS 45
Methods for evaluating submitted cost-effectiveness models 45
Submitted model 46
Patient population 47
Choice of comparator 47
Type of analysis and decision model 47
Clinical and epidemiological data 48
Efficacy 48
Radiologist reading times 49
Safety 49
Costs 50
Health related quality of life 51
Our comments on the submitted parameters and input data 52
Cost-effectiveness results 54
Sensitivity analyses 54
Budget impact analysis 55

DISCUSSION 58
Clinical effectiveness 58
Our findings compared to those of other reviews 59
Comments 60
Cost-effectiveness 63

CONCLUSION 65

REFERENCES 66

APPENDIX 71
Appendix 1 List of ongoing studies reported by submitter 71
Appendix 2 Norwegian Institute of Public Health's search strategies 73

Preface

What is a single-technology assessment

A single-technology assessment is one of a series of health technology assessment (HTA) products that can be mandated in "The National System for Introduction of New Health Technologies" within the Specialist Health Service in Norway (https://nyemetoder.no/).

Within this system, the Commissioner Forum RHA ("Bestillerforum RHF") evaluates submitted suggestions and decides on which technologies should be assessed and the type of assessment needed. In a single-technology assessment, the technology (a pharmaceutical or a device) is assessed based on documentation submitted by the company owning the technology or its representatives ("the submitter").

The HTA unit of the Norwegian Institute of Public Health (NIPH) receives and evaluates the submitted documentation, but is not the decision-making authority. Single-technology assessments conducted at NIPH are published on our website (www.fhi.no) and https://nyemetoder.no/

Objective

This single-technology assessment was commissioned by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. The objective of this single-technology assessment is to assess the efficacy, safety (radiation risks), and cost-effectiveness of digital breast tomosynthesis in breast cancer screening in Norway.

Log

We received the commission regarding "*Three dimensional digital breast tomosynthesis in screening for breast cancer"* ID2015_041 on January 25, 2016. "Bestillerforum" requested the National Institute of Public Health's HTA Unit, to perform a clinical effectiveness and safety assessment along with a cost-effectiveness analysis

of this single-technology (device). Information about the commission can be seen ere:
https://nyemetoder.no/metoder/tredimensjonal-digital-brysttomosyntese-dbt-i-screening-for-brystkreft

Date	Correspondence
September 25, 2015	Publication of horizon scanning report on this device
January 25, 2016	The commissioning forum commissioned a single-technology assessment
March 2016 – October 2016	Dialogue and meeting with concerned company
December 14, 2016	Valid submission acknowledged
April 28, 2017 – May 5, 2017	Norwegian Institute of Public Health external review process
May 12, 2017	Norwegian Institute of Public Health internal review process
June 12, 2017	End of 180 days evaluation period

Project group

The project group:
Norwegian Institute of Public Health:
Espen Movik, health ecomonist
Therese Kristine Dalsbø, senior advicer
Lise Lund Håheim, senior researcer
Åse Skår, senior advicer
Beate Charlotte Fagerlund, health economist
Elisabet Vivianne Hafstad, research librarian
Norwegian Radiation Protection Authority:
Eva Godske Friberg, radiation expert

We gratefully acknowledge help and feedback from the following individuals:

External clinical expert:
Professor Solveig Hofivnd, leader of the Norwegian Breast Cancer Screening Program.

External reviewers:
Marit Muri Holmen, radiologist, Oslo University Hospital
Hildegunn Siv Aase, radiologist, Haukeland University Hospital

Signe Agnes Flottorp	Ingvil Sæterdal	Espen Movik
Department director	*Head of unit*	*Project coordinator*

List of abbreviations

2D	Two-dimensional (mammogram)
3D	Three-dimensional (tomosynthesis)
AGD	Absorbed dose to granular tissue
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Cancer detection rate
CISNET	Cancer Intervention and Surveillance Modeling Network
CUA	Cost utility analysis
DBT	Digital breast tomosynthesis
DM	Digital mammography
DPCP	Detectable preclinical phase
DCIS	Ductal carcinoma in situ
FFDM	Full field digital mammography
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
IARC	International Association for Research on Cancer
LCIS	Lobular carcinoma in situ
NBCSP	Norwegian Breast Cancer Screening Programme
NOK	Norwegian kroner
OTST	Oslo Tomosynthesis Screening Trial
PICO	Population, Intervention, Comparator, Outcome
RHA	Regional Health Authority
S2D	Synthetic two dimensional (mammogram)
STA	Single-technology Assessment
TNM	Tumor, Nodes, Metastases
US	United States

Background

Name of the device and the manufacturer responsible for the submission

Name of device:
The Selenia® Dimensions® 9000 mammography and breast tomosynthesis system.

Name of the manufacturer who has submitted the application:
Hologic, Inc.
Hologic Mammography Products are distributed in Norway by Tromp Medical B.V. through Mebi AS.

A note on the single-technology assessment (STA) format

Hologic, Inc. is, to date, the only manufacturer that has submitted a documentation pack in response to the Commissioner Forum RHA's request for an assessment of digital breast tomosynthesis equipment for breast cancer screening. As this report is a single-technology assessment (STA), it is restricted to cover the efficacy, safety and cost-effectiveness of the Selenia Dimensions® DBT system, and only the system versions described in the included studies. The reason for this is that the technology is continuously under development. This report is not a comprehensive assessment of the digital breast tomosynthesis technology as such.

Current use

Digital breast tomosynthesis is currently used in Norway as a diagnostic method when there is clinical suspicion of breast cancer or as follow-up after positive findings in routine breast cancer screening with digital mammography (1). A technology assessment of the use of DBT for diagnostic purposes was one of the proposals put

forward to the Commissioning Forum ("Bestillerforum RHF)[1]. However, this area of use is not assessed in this report since no documentation pack relevant for diagnostic use has been submitted.

The Hologic Selenia® Dimensions® BT system was approved in the European Union (EU) with Conformité Européenne (CE) marking in 2008, and by the United States Food and Drug Administration (USFDA) in 2011 (1). The term "approved" is, in this context, understood to imply that the system meets national technical and quality standards and not necessarily that it has undergone a formal health technology assessment process. We know of one HTA of DBT that was performed by the Canadian HTA agency (CADTH) in 2015 (2). According to the submitter, the method is currently approved for diagnostic use in over 50 countries. To our knowledge, DBT is not currently used as part of a publicly financed national screening programme in Europe. However, follow-up studies offering DBT to the entire target population are now running in designated regions in Italy and Spain. A number of Hologic machines have recently been purchased for the breast cancer screening program in the Netherlands. Until the evidence regarding DBT in screening is more closely considered the system will be used for screening with DM (Solveig Hofvind, personal communication).

Description of the technology

Digital breast tomosynthesis involves a series of low-dose exposures from an X-ray tube moving in an arc over the breast. As in full field digital mammography (DM), the breast is compressed between a plastic compression plate and a developing platform (1). The images from successive exposures can then be digitally constructed to obtain a detailed 3D image. The newer tomosynthesis systems also make it possible to construct a "synthetic" 2D image comparable to a standard digital mammogram. The Oslo Tomosynthesis Screning Trial (OTST) has shown that the test performance values associated with synthetic 2D images are similar to those of standard 2D images when used in combination with DBT (3;4). This means that "synthetic 2D" and 3D images can be captured on the same machine in the same session and with the same breast compression time as a DM alone.

One of the disadvantages of traditional 2D mammography is the frequent distortions in breast structure due to overlapping signals originating at different tissue depths (1;5). This may prevent disease detection and lead to false negative findings. Conversely, it may suggest disease where none exists and lead to false positive

[11] See "New Health Technologiess" (Nye Metoder) website: https://nyemetoder.no/metoder/tredimensjonal-digital-brysttomosyntese-dbt-i-screening-for-brystkreft

findings (1). The sensitivity of mammography decreases with breast density as overprojection of tissue can hide the presence of tumors. The probability of such a masking effect increases the more glandular tissue the breast contains (5). Mammographic dense breast tissue is mainly a problem in younger, premenopausal women, but also in postmenopausal women who may or may not be on hormone replacement therapy. Overprojection may also lead to false positive cases either by making it difficult to detect the typical boundaries of a benign lesion or by the projection of normal structures on top of each other which may cause suspicion of a malignant lesion (5). DBT is a 3D imaging process with the potential to improve mammographic precision by reducing the effect of overprojecting tissue (5).

The pseudo-3D image created by the movement of the X-ray tube in an arc over the detector provides information in an additional dimension in multiple high-resolution "slices" (1). The angular diameter and angular distance between each exposure will affect image resolution and processing time and thus radiation exposure (5). There are several DBT systems on the market today, which vary with regard to certain characteristics. For example, the angular diameter in DBT systems varies among manfacutrers of DBT from +/- 7.5 degrees to +/- 25 degrees. In addition, the technology is constantly evolving.

Breast cancer epidemiology

The latest available national cancer statistics (6) show that 3 415 women were diagnosed with breast cancer in 2015. Breast cancer is the predominant form of cancer among women in the overall female population (22% of female cancer incidence in 2011-15), particularly in the 59-69 age bracket (29% in the same period) (6). Estimates suggest that just over half of the newly diagnosed cases in the 2011-15 period came from this age group[2]. There is some regional variation: The highest age-adjusted incidence of breast cancer for the years 2009-2013 was in Oslo with 85.5 per 100,000. The lowest was in Finnmark with 58.5 per 100,000 (7).

Breast cancer can be curable if detected and treated at an early stage. Five-year survival was 89% overall in the 2011-2015 period, and 26% for metastatic disease (stage IV). A total of 585 women died of breast cancer in 2015 (8). 44,182 persons diagnosed with breast cancer were alive in Norway at the end of 2015, while the corresponding figure for the end of 2005 was 31,364 (6).

[2] Kreftregisteret (Cancer Registry of Norway), Cancer in Norway 2015 tables 10b and 12b: An average of 52,4% new cases of breast cancer in 2011-2015 occurred in the 50-69 age group

Breast cancer screening

Terms used to describe screening outcomes

The following endpoints with respect to test performance were considered to be of importance for this report. Measures used for diagnostic purposes are included so as to make a distinction from screening, for example the World Health Organization's definitions (9). Diagnostic status for breast cancer is verified by a diagnostic work-up involving further testing.

Screening for the validity of a diagnostic test; definitions:

Sensitivity: The ability of the test to identify correctly those who have the disease (the probability of a positive test among persons with the disease)

Specificity: The ability of the test to identify correctly those who do not have the disease (the probability of a negative test among persons who do not have the disease).

False positive rate (FP): The probability of a positive screening test among persons who does not have the disease.

False negative rate (FN): The probability of a negative screening test amongpersons who have the disease.

Predictive value of a diagnostic test used in screening:

Positive predictive value (PPV): The probability of correctly identifying persons with the disease among persons with positive screening tests. PPV has also been used to quantify the probability of a positive test at recall or at biopsy.

PPV1 in a breast cancer screening setting refers to the number of breast cancer cases among those who have been recalled for further examination (i.e. those who tested positive at the screening). PPV2 refers to the number of breast cancer cases among those who have undergone a biopsy.

Negative predictive value (NPV): The probability of correctly identifying persons without the disease among persons with negative tests.

Prevalence of the disease: The rate of occurrence of a disease in a specified population and time period.

For a diagnostic test to be considered valid in a screening program, it must have a sufficiently high sensitivity and specificity. The prevalence of a disease is relevant to defend the use of a diagnostic test in a non-diseased population, considering its potential risks. Low prevalence reduces the PPV, and increases the false positives.

Cancer occurrence and detection:

Interval cancer rate: The rate of occurrence of diagnosed cancer between two regular screening examinations, where the last screening test was negative.
Cancer detection rate: The rate of all cancers detected in the course of a screening.

Over- and underdiagnosis

One of the challenges of breast cancer screening is that some of the lesions detected might never develop into symptomatic disease during the patient's lifetime. This leads to unnecessary treatment, associated costs and reduced quality of life. The Research Council of Norway's evaluation of the Norwegian Breast Cancer Screening Programme from 2015 concluded that: "We consider the most reliable estimates of overdiagnosis of invasive breast cancer and DCIS combined, for women aged 50-79 years compared to a situation without screening, to be within the range 15-25%" (10). On the other hand, the occurrence of interval cancers, that is, cancer diagnosed between screening visits, may indicate a degree of underdiagnosis since some tumors may have been missed at the last mammography (11). Although some interval cancers represent highly malignant tumors that grow very fast and were not detectable at the previous mammography.

The Norwegian Beast Cancer Screening Program

As breast cancer is the most common cause of cancer death among women globally, many high-income countries have introduced population based mammography screening (12). The objective of such programs is to reduce mortality among those invited and screened by detecting tumors at an early stage while the disease is curable. Analyses have shown a relative reduction in breast cancer mortality of 20-30% among those invited to mammography screening programs and approximately 40% among those actually attending (10).

The Norwegian Breast Cancer Screening Program is a publicly funded screening service offered every other year to women aged 50 to 69. Study results suggest a reduction in mortality of 43% among those attending compared to those who do not (13). The Norwegian Breast Cancer Screening Programme was first established in four counties in 1996 and expanded to a nationwide programme in 2005 (14). The Cancer Registry of Norway is responsible for the planning and implementation of the programme. This involves invitations, IT and registration, quality assurance, information, evaluation and international cooperation. In 2017 there are 23 stationary and 4 mobile screening units where the mammography examination takes place. There are 16 breast diagnostic centers at which interpretation of the screening mammograms and diagnostic follow-up take place. The actual screening is conducted by the Regional Health Authorities, which also are responsible for diagnostic follow-up

and treatment. From January 1st, 2017, they are also responsible for technical and physical quality assurance with respect to the equipment used in the screening process (12).

The 50-69 age-group has been singled out for screening because the risk of breast cancer is relatively high in this group, with eight of ten cases of breast cancers detected in women above age 50. Due to a lower prevalence rate in the younger age group, more women in this group would have to be screened to attain the same level of cost-effectiveness (12). Moreover, mammographic images are more difficult to interpret for younger women, which means that more follow-up is required in order to detect disease. The WHO has recently put forward evidence to suggest that screening may also be worthwhile in women aged 70-74. The Cancer Registry of Norway is open to a discussion on the matter, though no conclusion has yet been drawn (12). At present, women can expect to receive 10 screening invitations during the course of their lifetime. A total of 578 000 invitations were sent out in the period 2014-2015, of which 435 000 were accepted (75% acceptance rate). The acceptance rate seems to remain relatively stable at this level over many years, with some variations between counties (15). A visit to a breast screening center normally takes 10-20 minutes, of which the actual image capturing takes about 5 minutes (12). Images are currently captured in 2D from two angles for both breasts. Two breast radiologists at the center independently read the mammograms. If there is disagreement, a consensus meeting is held to decide whether to recall the woman or not. Generally, patients receive screening results within two to three weeks.

If the results are inconclusive or suggest the presence of disease, the patient will be called back for further assessment to confirm or rule out abnormal findings. These normally involve new mammographic images, and/or ultrasound or DBT and a needle biopsy or cytology in about 50% of the recalled women (12). In 2013-2014, 11 460 cases were subject to follow up, of which 2 360 cases of invasive breast cancer or DCIS (ductal carcinoma in situ, pre-cancer stage) were detected. About 20% of the recalled women were diagnosed with breast cancer.

Patient co-payment for screening and follow-up visits are currently NOK 245 per visit. This sum is not to be incorporated into the total annual patient co-payment costs, which are reimbursed over a given limit. Travel costs to the screening unit have to be covered by the women (15).

Technology in current use

Full-field digital mammography, which is used at all screening and diagnostic units in Norway today, gradually replaced analogue screen-film mammography (SFM) in the period 2000-2011 (14). DM offered reduced radiation exposure and a lower rate

of recalls due to technical failure. Moreover, it allows for a simplified storage, workflow and computer assisted detection (16) . Patient recall rates were reduced following the transition, while the positive predictive value of follow-up diagnostics increased (16). Interval cancer rates remained stable.

Radiation exposure

Full-field digital mammography and digital breast tomosynthesis both make use of ionizing radiation and, as a consequence, are associated with radiation-induced harm. The female breast is identified as a radiosensitive organ. The risk for radiation-induced breast cancer incidence and mortality is strongly dependent on the age at exposure and assumed to be linear with the accumulated dose to the breast. In screening programs it is important to ensure a net positive effect, weighing the clinical benefits against the radiation-induced harm. An increase in dose and risk can be accepted if it is outweighed by an increase in clinical benefit. Replacing DM with DBT in combination with DM, as evaluated in most of the studies included in this report, will typically increase the total dose to the breast, and the associated risk, by a factor of between 2.23 and 2.37. This increase in risk can only be justified by an increase in clinical benefits such as increased cancer detection rate, reduced number of false positive and false negative readings and a reduced recall-rate. Other harms such as under- and overdiagnosis must also be taken into account.

DM and DBT or DM alone in breast cancer screening

DBT is considered for use in combination with digital mammography in breast cancer screening in Norway. There is good evidence to suggest that DBT in addition to DM used in a clinical context provides increased accuracy compared to DM alone, in the form of increased detection of breast cancer (17;18). Based on this, DBT may have the potential to increase accuracy in breast cancer screening as well. Prospective screening trials and retrospective evaluations have shown that adding DBT to or instead of standard digital mammography generally improves screening detection measures compared to standard mammography alone. However, estimates of the effect of DBT on detection measures vary between studies, reflecting the variability in study methodology, screening settings and populations. (19). Most of the large prospective studies conducted in a screening context compare DBT in addition to DM / S2D with DM alone. All the identified studies in our report use the combination of DBT and DM /S2D as the intervention arm. According to experts (Solveig Hofvind, personal communication) this is due to DBT used alone is unlikely to be used as a screening method. If one were to introduce DBT in a mammography screening program, one would still have to carry out digital mammography in order to enable comparison with previous DM pictures. Moreover, microcalcification in the breast tissue is an important malignancy sign, and is not visible in the same way with DBT as it is with DM (20).

As noted previously in this report, the new generation of tomosynthesis systems will make it possible to construct a synthetic two dimensional (S2D) image comparable to a standard digital mammogram in the same machine (21). This will make it unnecessary to use two separate systems.

However, one cannot assess what potential DBT has as a technology in a screening context on the basis of studies from clinical settings. The introduction of DBT in combination with DM also has the potential to increase overdiagnosis due to the higher detection rate. Currently one cannot determine in advance which tumors will develop to cause a symptomatic and life threatening disease. Every detected malignant tumour has to be treated. The interval cancer rate is therefore of great importance for evaluation of the efficacy of DBT in breast cancer screening programmes. Given the relatively low incidence of breast cancer, it is difficult to estimate the impact of screening on total mortality. Breast cancer related survival has improved during the last decades, probably due to both organized screening programs and more effective treatment of the disease (22) . In order to clarify whether the results from clinical mammography are transferable to screening, results are required from dedicated screening studies.

Earlier recommendations

The advisory board in the Norwegian Breast Cancer Screening Program published a status report in December 2015, entitled "Tomosyntese i mammografiscreening" (5). The report concluded that at present, there was insufficient evidence regarding the effects of DBT in combination with DM to make a decision about whether or not to implement DBT as a routine screening method in the Norwegian Breast Cancer Screening Programme.

The WHO International Agency for research on Cancer (IARC) (23;24) considered in an evaluation from 2015 breast cancer screening with DM+DBT compared to DM alone, and concluded that there was sufficient evidence regarding an increase in the detection rate of cancers, limited evidence regarding false-positive screening outcomes and inadequate evidence regarding both reduction in the rate of interval cancers and breast cancer mortality. The authors found that there was sufficient evidence with respect to an increase in the radiation dose when using both DBT and DM together (dual acquisition).

The European Society of Breast Imaging (58) recently recommended that women should receive information about the potential advantages of tomosynthesis in terms of increased detection rate and reduced recall rate as well as information about the modest increase in radiation dose.

Clinical effectiveness

The main research questions

Based on the original proposal and the subsequent commission from the Commissioner Forum RHA ("Bestillerforum RHF"), the purpose of this report is to investigate DBT for use in breast cancer screening. The main research questions are organized according to the relevant inclusion criteria structured as PICOS (P= Population, I= Intervention, C= Comparator, O=Outcomes (Endpoints), S=Study design) shown in Table 1 below.

Table 1. *Main research questions of the single technology assessment on tomosynthesis*

PICO	Defining items
Population	Women who participate in a population based breast screening program
Intervention	• Tomosynthesis (DBT)* • DBT* + synthetic DM (S2D)* • DBT* + DM (by standard equipment)
Comparator	DM (standard equipment)
Outcomes	• Recall rate (RR) • Cancer detection rate (CDR) • Interval cancer rate (ICR) • False positive rate (FPR) • False negative rate (FNR) • Sensitivity • Specificity • Mortality (total mortality, breast cancer mortality) • Quality of life
Study design	Prospective controlled studies: • Randomized controlled trials • Quasi randomized controlled trials • Controlled cohort studies

* performed by Hologic 3D Mammography™ Selenia® Dimensions® System

Literature searches and identification of relevant published literature

1. The submitter's documentation pack

Critical appraisal of the submitter's literature searches

We assessed the submitted literature search by Hologic according to our inclusion criteria (PICOS), search terms and databases used. The submitter searched 14 sources covering years from inception to 11/07/16. We found the search strategies and selection of databases satisfactory, but performed an updated literature search in February 2017 in order not to miss articles published during the last months.

Critical appraisal of the submitted literature and ongoing studies

Hologic identified 12,530 publications and an additional 32 publications through other sources. After removing duplicates 7,969 references remained to be screened. Of these references 7,855 non-relevant studies were excluded. The remaining 114 references were assessed in full text. The final result was 12 studies. These are presented in 23 publications plus four additional publications, a total of 27 publications, according to the submitter's inclusion and exclusion criteria. We have included 12 publications from four of these studies in accordance with our main research questions (Table 2).

Table 2. *List of studies included by Hologic, type of study design and reason for inclusion or exclusion according to inclusion criteria applied in this report/our inclusion criteria*

Study name or location (reference)	Study design		
		Reason for inclusion	Reason for exclusion
PROSPR (Population-Based Research Optimizing Screening through Personalized Regimens) initiated by National Cancer Institute (NCI), US, including three study sites namely University of Pennsylvania, University of Vermont, and Geisel School of Medicine at Dartmouth in conjunction with Brigham and Women's Hospital. (Conant 2016)	Prospective study with a retrospective cohort, multisite, multi-reader	Correct according to our PICOS	
PROSPR - UPEN - University of Pennsylvania, US (McDonald 2016, McDonald 2015, Zuckerman 2015)	Prospective study with a retrospective cohort, one site, multi-reader	Included in PROSPR but reports results separately	

US (Destounis 2014)	Retrospective, one site		Retrospective study
US Mulitcenter trial (Rafferty 2016, Durand 2015, Friedewald 2014, Greenberg 2014, Haas 2013, McCarthy 2014, Rose 2013, Rose 2013)	Retrospective, one site, multi-reader.		Retrospective study
US (Laurenco 2014)	Retrospective, multi-reader		Retrospective study
Malmø, Sweden (Lang 2016, Lang 2016)	Prospective, one site, multi-reader.		Equipment from Siemens
OTST, Oslo University hospital, Oslo, Norway (Skaane 2013 Radiology and Eur radiol, Skaane 2014)	Prospective, one site, multi-reader	Correct according to our PICOS	
STORM, Italy (Bernardi 2014, Caumo 2014, Ciatto 2013, Houssami 2014)	Prospective, two sites, multi-reader	Correct according to our PICOS	
STORM-2, Italy (Bernardi 2016)	Prospective, one site, multi-reader	Correct according to our PICOS	
US (Sumkin 2015)	Retrospective study.		Retrospective study. High level of high risk patients in DBT-arm of study
US (Sharpe 2016)	Retrospective study.		Retrospective study. High level of high risk patients in DBT-arm of study
TOMMY, UK (Gilbert 2015)	Retrospective study		Retrospective study. About diagnostic accuracy

Critical appraisal of the submitter's identification of ongoing studies

The submitter supplied a list of 33 ongoing clinical trials of Food and Drugs Administration-approved, CE-marked, and non-commercial DBT systems per May 26, 2016, registered with either ClinicalTrials.gov or the EU Clinical Trial Registry (see list in Appendix 1). Our review of this list determined that only one of these trials pertains to Hologic and the system assessed in this report. The objective of this particular study (NCT01852032) however, is to compare DBT with CT for patients with suspected breast cancer, i.e. not a screening intervention.

The Oslo study, OTST, finished data collection in 2012. The final outcome of this study is expected to be published later in 2017. There is a coordinated screening with the hospital board of Vestre Viken and the county of Vestfold using the Hologic equipment. There is a study on the use of tomosynthesis in progress in Bergen using equipment provided by General Electric.

2. Updated search by the Norwegian Institute of Public Health

We ran search updates in the following databases with only minor changes to the strategies used by the submitter:

- ClinicalTrials.gov
- Cochrane Central Register of Controlled Trials (Wiley)
- Cochrane Database of Systematic Reviews (Wiley)
- Embase (OVID interface)
- Health Technology Assessment Database (Wiley)
- International Clincial Trials Registry Platform (ICTRP)
- LILACS
- MEDLINE (OVID interface)
- PubMed (National Library of Medicine) subset PubMed not MEDLINE – added for the updated search
- Web of Science Core Collection

Like the submitter, the project team also checked the webpages of NICE and NHS Breast Screening Programme.

A medical librarian (EH) planned and executed all searches. The updated searches identified 1,125 unique references added to the databases from July 2016 to February 2017.

Appendix 2 reports the complete search strategies.

Two reviewers (LLH and TKD) independently assessed the citations with abstracts according to the previously defined inclusion criteria (Table 1). Both reviewers assessed the relevant references for inclusion in full text. We did not include any of these studies as they did not fulfill all of our inclusion criteria.

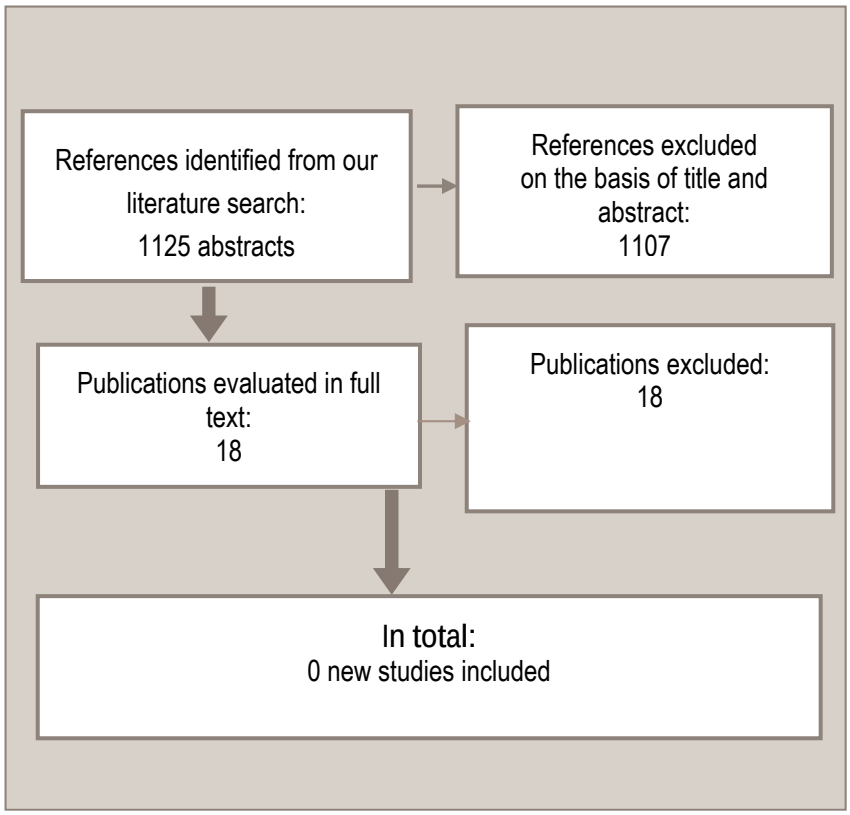

Figure 1. *A flow chart of our selection of literature*

Identification of relevant health technology assessments

No new HTA-report has been identified.

Characteristics of included studies

We included the following prospective controlled studies from the documentation pack submitted by Hologic:

- PROSPR (Population-based Research optimizing Screening) from USA
- OTST (Oslo Tomosynthesis Screening Trial) from Norway
- STORM (Screening with Tomosynthesis OR standard Mammography) and STORM-2 from Italy

We collected the available information from the documentation pack about these studies and they are also briefly summarized in Table 3 below.

Table 3. *Study characteristics of the included studies*

Study name (country)	Study design (references)	Age and number of participants	Intervention	Comparison
PROSPR (USA)	Prospective study with a retrospective cohort, multisite. (Conant 2016, McDonald 2016) (25;26)	Age 40-74 55,998 DM+DBT 142,883 DM only	DM+DBT	DM
OTST (Norway)	Prospective, one site. (Skaane 2013, Skaane 2013) (3;27)	Age 50-69 12,621	DM+DBT	DM
	Prospective, one site. (Skaane 2014) (21)	Age 50-69 Study period 1: 12,621 DM+DBT and initial 2SDM +DBT Study period 2: 12,270 DM+DBT and current 2SDM +DBT	s-DM +DBT	DM+DBT
STORM (Italy)	Prospective, two sites. (Bernardi 2014, Caumo 2014, Ciatto 2013, Houssami 2014) (28-31)	Age 48-71 7,292	DM+DBT	DM
STORM-2 (Italy)	Prospective, one site. (Bernardi 2016) (4)	Age 47-74 9,672	DM+DBT or s-DM+DBT	DM

PROSPR

Design. The study was funded by the National Cancer Institute, US, to evaluate and improve the breast cancer screening processes by conducting multi-site, coordinated, transdisciplinary research (25). It was conducted at ten sites, but the PROSPR study team presented summarized results from three sites. Interval cancer was reported by UPEN (University of Pennsylvania) (32). Data collection was from 2011 to 2014. PROSPR (Population-based Research optimizing Screening).

Population. Women aged 40-74 with no known history of breast cancer and no other breast imaging within 3 months prior. Total population with digital Mammography (DM) examinations was 142,883 women. Total population with DBT in combination with DM examinations was 55,998 women.

Endpoints. The results were assessed for consecutive years. Recall rates, biopsy rates, breast cancer rate, cancer detection rate (CDR), false negative rate, positive predictive value for cancer /recall, sensitivity, specificity, interval cancer from the UPEN-part of the study.

OTST
Design. This a prospective trial for DM and DBT in combination to compare individually differences at screening for breast cancer, Oslo, Norway (3;21;27). Equipment and support was provided by Hologic.
Population. Women aged 50-69 who were enrolled as they took part in the national mammography screening program, a population based screening program. Period 1 from Nov 2010 to December 2011 used early version of software to construct synthesized DM images (2SDM). Period 2 from January 2012 to December 2012 used later version of software to construct synthesized DM images (2SDM).
Endpoints. Recall rate, rate of screen-detected breast cancer (SDC), false positive rate (FPR).

STORM
Design. A prospective population based trial of mammography screening of DM+DBT versus DM in Trento and Verona, Italy (28-31). Equipment was provided by Hologic.
Population. Women aged 48-71 years.
Endpoints. Recall rate, CDR, incremental CDR, false positive recall.

STORM-2
Design. A prospective population based trial of mammography screening of DM versus DM +DBT versus 2sDBT + DBT in Trento, Italy (4). There was no funding source reported.
Population. Women aged 47-74 years taking part in the Trento screening program.
Endpoints. CDR, false positive recall.

Risk of bias in included studies

The risk of bias assessment of the included studies was conducted by Hodgson and colleagues (33) for OTST and STORM, and by Hologic for PROSPR and STORM-2. They used the 11 items from the QUADAS-2 Tool (table 4). According to the documentation pack page 40, most studies in cases of positive screening results used standard procedure to perform follow-up imaging and fine needle, core, or excisional biopsy as the reference standard for diagnostic purposes. Due to the invasive nature of breast biopsy, only women with positive screening results received this reference standard, allowing for potential bias due to partial verification. Breast biopsy is only offered to and performed on women with positive screening results, so the

outcome assessments were not blinded in these cases. These potential areas of bias are difficult to avoid in mammography screening studies.

Hodgson and colleagues (33) assessed the overall risk of bias in the included OTST and STORM studiesas low in theirsystematic review. The overall risk of bias in the PROSPR and STORM-2 was also low as assessed by Hologic. We have presented the risk of bias assessment for the included studies in Table 4 below.

Table 4. *Risk of bias (QUADAS-2) of included studies according to Hodgson and Hologic*

	PROSPR†	OTST*	STORM*	STORM-2†
Representative spectrum?	+	+	+	+
Acceptable reference standard?	+	+	+	+
Acceptable delay between tests?	?	+	+	?
Partial verification avoided?	?	-	-	-
Differential verification avoided?	-	+	+	-
Incorporation avoided?	+	+	+	+
Reference standard results blinded?	-	-	-	-
Index test results blinded?	?	+	+	-
Relevant clinical information?	+	+	+	+
Uninterpretable results reported?	?	?	?	?
Withdrawals explained?	+	+	+	+

(+)=positive assessment and low risk of bias; (–)=negative assessment and moderate to high risk of bias; (?)=insufficient information and/or unclear risk of bias.

**Assessments conducted by Hodgson et al, 2016; †assessments conducted by Hologic.*

Results

We have presented the results from the documentation pack submitted by Hologic. We have extracted data and presented them in Table 5 below for these outcomes:

- Recall rate
- False positive rate
- Cancer
- Sensitivity/ specificity
- False negative rate
- Death and Quality of Life

Table 5. *Results from the included studies*

Study	Recall rate	False positive rate	Cancer	Sensitivity/ specificity	False negative rate	Death and Quality of Life
PROSPR						
Conant 2016*	DM: 10.4% DM+DBT: 8.7% (18% decrease-unadjusted, *P*<0.0001, 32% decrease-adjusted)	NR	Cancer detection rate: DM: 4.4 per 1,000 exams DM+DBT: 5.9 per 1,000 exams (*P*=0.0026) Invasive CDR: DM: 3.3 per 1,000 exams DM+DBT: 4.2 per 1,000 exams (*P*=0.0449)	Sensitivity: DM: 90.6% DM+DBT: 90.9% Specificity: DM: 89.7% DM+DBT: 91.3% (*P*<0.0001)	False negative rate: DM: 0.46/1,000 DM+DBT: 0.6/1,000 (*P*=0.347)	NR
UPen McDonald 2016	NR	NR	Interval cancer rate: Year 1: DM: 0.7% DM+DBT: 0.5% (P= 0.60)	NR	NR	NR
OTST						
Skaane 2013 Radiology First interim analysis	DM: 265/12,621; 2.1% DM+DBT: 351/12,621; 2.78% (p<0.72)	DM: 771/12,621; 6.11% DM+DBT: 670/12,621; 5.31%	Cancer detection rate: DM: 77/12,621; 0.61% DM+DBT: 101/12,621; 0.80% Invasive CDR: DM: 56/12,621; 0.44% DM+DBT: 81/12,621; 0.64%	NR	NR	NR
Skaane 2013 Eur Radiol Second interim analysis	DM: 365/12,621; 2.9% DM+DBT: 463/12,621; 3.67% (p=0.005)	DM: 1286/12,621; 10.3% DM+DBT: 1057/12,621; 8.5% (p<0.001)	Cancer detection rate: DM: 90/12,621; 0.71% DM+DBT: 119/12,621; 0.94% (p<0.001) Invasive CDR: DM: 67/12,621; 0.53% DM+DBT: 94/12,621; 0.74%	NR	NR	NR

Study	Recall rate	False positive rate	Cancer	Sensitivity/ specificity	False negative rate	Death and Quality of Life
Skaane 2014 Radiology Third interim analysis	NR	Period 1: DM+DBT 5.3% s-DM+DBT 4.6% (p=0.012) Period 2: DM+DBT 4.6% s-DM+DBT 4.5% (p=0.85)	Cancer detection rate: Period 1: DM+DBT 8.0 per 1000 s-DM+DBT 7.4 Per 1000 Period 2: DM+DBT 7.8 per 1000 s-DM+DBT 7.7 per 1000	NR	NR	NR
STORM						
Ciatto 2013	DM: (322+39)/7,294; 4.9% DM+DBT: (254+59)/7,294; 4.3%	DM: 322/7,294; 4.4% DM+DBT: 254/7,294; 3.5%	Cancer detection rate: DM: 5.3 (3.8 to 7.3) per 1,000 screens DM+DBT: 8.1 (6.2 to 10.4) per 1,000 screens Incremental CDR per 1000 screens compared to DM: 2.7 (95% CI: 1.7-4.2)	NR	NR	NR
STORM-2						
Bernardi 2016	NR	DM: 3.42% (95% CI: 3.07 to 3.80) DM+DBT: 3.97% (95% CI: 3.59 to 4.38) Synthetic DM+ DBT: 4.45% (95% CI: 4.05 to 4.89)	CDR per 1,000 screens: DM: 6.3 (95% CI: 4.8 to 8.1) DM+DBT: 8.5 (95% CI: 6.7 to 10.5) s-DM+DBT: 8.8 (95% CI: 7.0 to 10.8) Incremental CDR per 1,000 screens to DM alone: DM+DBT: 2.2 (95% CI: 1.2 to 3.3) s-DM+DBT: 2.5 (95% CI: 1.4 to 3.8)	NR	NR	NR

DBT=breast tomosynthesis; s-DM=synthetic DM breast tomosynthesis; CDR=cancer detection rate; CI=confidence interval; DM=digital mammography; NR=not reported

Summary of findings – clinical effectiveness

We found no meta-analysis in the documentation pack submitted by Hologic. We assessed overall confidence in the results for each endpoint using GRADE (Grading of

Recommendations Assessment, Development, and Evaluation) because this was not done by Hologic in their documentation pack.

We followed the guidelines provided by the GRADE working group and categorized our confidence in the results into four levels: high, moderate, low and very low. A more detailed description of this system is available through their website http://www.gradeworkinggroup.org/ and in the Cochrane Handbook available at http://handbook.cochrane.org/

We have made a plain language summary of the findings for each relevant outcome.

We found that compared to digital mammography alone, the use of Hologic digital breast tomosynthesis in combination with digital mammography or synthesised digital mammography:

- We are uncertain if Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography decreases or increases **recall rates** compared to digital mammography alone (very low confidence due to conflicting evidence from observational studies).
- May increase the rate of **screening-detected cancer** (cancer detection rate - CDR) according to all studies (very low confidence due to sparse evidence from one observational study).
- We are uncertain if Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography makes any difference for detection of **interval cancer** compared to digital mammography alone (very low confidence in the evidence due to sparse evidence from one observational study).
- We are uncertain if Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography decreases or increases **false positive rates** compared to digital mammography alone (very low confidence due to conflicting evidence from observational studies).
- May provide similar **sensitivity** rate, but may increase **specificity** rate (low confidence due to evidence from observational studies)
- We are uncertain if Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography decreases or increases **false negative rates** compared to digital mammography alone (very low confidence due to sparse evidence from one observational study).
- Information on **death** and **quality of life** was not reported.

Uncertainty about the effects means that new research may alter our conclusion.

Radiation dose and risk assessment

Justification of medical exposure – clinical benefits versus radiation detriments

New types of practices involving medical exposure must be justified in advance before being generally adopted, according to the national radiation protection regulation (34). This requirement is in compliance with the new European directive on radiation protection, Council Directive 2013/59/Euratom, (35). A new type of practice is considered justified if the medical exposure shows a net benefit, weighing the total potential diagnostic or therapeutic benefits against the detriment that the exposure might cause. Both direct benefits and risks to the health of an individual and to society should be evaluated and associated occupational and public exposure should be considered, when relevant. Efficacy, benefits and risks of available alternative techniques, which have the same objective but involve no or less exposure to ionizing radiation, should also be taken into account in the evaluation of justification of a new practice.

Radiation detriments are strongly dependent on the exposed organs, age at exposure and total accumulated dose. In assessing the radiation detriment, the following factors muse be addressed:

- Dose per examination and total accumulated dose (if more than one examination is performed) to patient and staff
- Estimate the risks related to the accumulated dose to patients and staff
- Identify if spesial radiosensitive organs (like breasts) or vulnerable patient groups (like children) are exposed

Radiation doses

Dose from mammography – average glandular dose (AGD)

In digital breast tomosynthesis (DBT), the X-ray tube rotates over a limited angular range and a low-dose exposure of the compressed breast is acquired every few degrees. The dose of interest in mammography is the average absorbed dose to the

glandular tissue (AGD). The AGD from DBT is the sum of the absorbed doses from all of the multiple low-dose projection images.

System related factors affecting the dose

The dose, and the corresponding image quality, is highly dependent on the design of the DBT system. Different vendors have adopted different solutions, resulting in different doses to the breast.

Factors affecting the dose and image quality from a DBT system are (36;37):

- Scan angle (varies between 10-50◦)
- Total number of projections (varies between 10-25)
- Type of detector (direct/indirect)
- Tube motion (continoues/step and shoot)
- Reconstruction algorithms (filtered back-projection (FBP)/iterative reconstruction)
- Actual scan parameters like tube voltage, exposure time and anode/filter combination will affect the dose depending on the size and composition of the breast

For the new generation of systems, actual scan parameters are determined by the automatic exposure control (AEC) according to the characteristics of the imaged breast (density and thickness). In older equipment, these parameters are set manually by the operator. In general, the dose increases with thicker breasts. DBT units have the possibility of operating in different modes, performing both DBT and DM uptakes. The newest generations of DBT systems have developed software that allows for generation of synthesized reconstructed 2D images (S2D). These images are expected to be comparable to the 2D images obtained from DM, and do not contribute to any assessed dose when generated. Equipment with the possibility of producing S2D images has the potential to reduce the total dose to the breast compared to DBT+DM, since S2D may replace the need for an additional DM.

Dose is dependent on the examination technique

The dose to the breasts will depend on the examination technique chosen. Both DBT and DM are normally performed in two views in screening, craniocaudal (CC) and mediolateral oblique (MLO).

When introducing DBT in mammography screening, different techniques have been explored:

DBT (one or two views) alone
DBT (one or two-views) in addition to DM
DBT (one or two views) in combination with S2D

Most of the clinical trials included in the documentation provided by the submitter, address the DBT (two views) in addition to DM (two views) or DBT (two views) in combination with the S2D images.

Reported doses from the clinical trials included in this report

The submitted documentation from the manufacturer did not give any information about doses and risks associated with the introduction of DBT in mammography screening. A review of the studies included in this report, identified that only the OTST and STORM-2 clinical trials reported information about doses to the breast (AGD) from DBT systems provided by Hologic (4;21). The equipment used in these trials was the Hologic Selenia Dimensions, both for DBT and DM examinations. The DBT system was equipped with AEC, a direct detector, a scan angle of 15◦ and 15 projections. The system was also equipped with the software "C-view" allowing for generating S2D images (4;21;37). The examination technique used in the trials was two-view DBT in combination with two-view DM or two-view S2D, compared to two-view DM, according to the defined inclusion criteria. The reported doses from these studies are summarized in Table 6 and the calculated dose ratios between the different techniques are presented in Table 7.

Table 6. *Average glandular dose (AGD) for different mammography techniques reported in the OTST and STORM-2 clinical trials (4;21).*

Study	DM	DBT	DBT+DM	DBT+S2D
OTST	1.58 ± 0.61 mGy (range: 0.74-4.51 mGy) (per view)	1.95 ± 0.58 mGy (range: 1.05-3.78 mGy) (per view)	3.52 ± 1.08 mGy (per view)	1.95 ± 0.58 mGy (range: 1.05-3.78 mGy) (per view)
STORM-2	1.36 mGy (per view)	1.87 mGy (per view)	3.22 mGy (per view)	1.87 mGy (per view)

The doses reported by the DBT system used in the clinical trials were similar when operating in DBT-mode, but the dose reported for the MD-mode was 22% higher in the OTST trial compared to the STORM-2 trial.

Table 7*. Dose ratio estimations for different mammography techniques reported in the OTST and STORM-2 clinical trials.*

Study	D_{DBT}/D_{DM}	D_{DBT+DM}/D_{DM}	$D_{DBT+S2D}/D_{DBT+DM}$
OTST	1.23	2.23	0.55
STORM-2	1.38	2.37	0.58

By introducing DBT as a stand-alone examination in mammography screening, the AGD will increase by 23% to 38% compared to DM. When DBT is used in combination with DM the doses will increase by a factor ranging from 2.23 to 2.37. However, by replacing the DM with S2D images the dose will be reduced by 42% to 45% compared with DM+DBT.

Evaluation of the doses reported in the OTST and STORM-2 studies

To evaluate the doses reported in the OTST and STORM-2 studies, we performed a literature search. We identified four relevant studies (37-40). A direct comparison of doses reported in these studies is, however, difficult because the studies were performed differently and the doses were often estimated in different ways. In general, the doses obtained in the OTST and STORM-2 trial are comparable to or slightly higher then doses and dose ratios reported in the identified relevant studies.

Svahn et al. performed a review of 17 clinical studies collecting information about the reported dose to the breast, which indicated that the dose ratio for DBT + DM compared to DM (D_{DBT+DM}/D_{DM}) ranged from 2.0 to 2.23 for the different vendors represented (37). This study indicates that the dose ratio from the Hologic Selenia Dimension system is among the highest dose ratios reported. Many of the clinical studies evaluated by Svahn reported doses from other examination techniques than the technique used in the OTST and STORM-2 studies. As expected, those studies evaluating one-view DBT + one-view DM and one-view DBT + two-view DM, all result in lower doses than two-view DBT + two-view DM. When the evaluating using DBT in mammography screening, it is therefore highly relevant to address whether other examination techniques that result in lower doses could be used.

Hauge et al. estimated the AGD from all DM systems used in the NBCSP in Norway in 2011 (38). Hologic was represented in this study with their older unit Hologic Selenia (only DM). In this study the unit from Hologic was associated with the highest dose to the breast compared to other vendors. The dose reported for DM from the Hologic Selenia Dimension in the OTST study were slightly higher, while the dose reported in the STORM-2 study was approximately 24% lower than the dose reported by Hauge et al. However, even though the doses are not directly comparable due to different generations of the Hologic systems, it is worth mentioning that the newest model does not always provide the lowest dose. The differences in the doses obtained in the OTST and STORM-2 trial is probably best explained by lack of optimization of the scan parameters or differences in breast thickness of the exposed women.

Maldera et al. have recently conducted a study where they compared doses to the breasts for different breast thicknesses represented by PMMA-phantoms, from four different manufacturers (39). For PMMA thicknesses ranging from 20 to 70 mm, the AGD values increased from 1.03 to 2.6 mGy for the Hologic Selenia Dimension. This study indicates the importance of also reporting the breast thickness associated with the reported AGD, since the mean AGD is highly dependant on the distribution of the breast thicknesses of the women represented in the different studies. Rodrigues et al. reported AGD from the Hologic Selenia Dimension to a 45 mm thick PMMA phantom to be 1.17 mGy and 2.09 mGy from DM and DBT, respectively, resulting in

a dose ratio of 1.79 (40). This dose ratio is much higher than the dose ratio reported in the OTST and STORM-2 study.

National diagnostic reference levels (DRLs) for mammography (DM)

The current national diagnostic reference levels (DRLs) for mammography screening (DM) in Norway is: AGD_{CC} = 1.46 mGy, AGD_{MLO} = 1.5 mGy and $AGD_{TOT\ (CC+MLO)}$ = 3.0 mGy (ref StrålevernInfo 2010). Doses from DM-uptakes performed by both Hologic Selenia and Hologic Selenia Dimensions have been reported to be above the national DRLs in Norway.

Radiation risk – induced breast cancer incidence and mortality

General

Radiation detriments related to medical exposures are mainly associated with harmful tissue reactions (deterministic effects) and late effects like radiation induced cancers and heritable effects (stochastic effects) (41).

The induction of tissue reactions is generally characterized by a threshold dose. Above the threshold dose the severity of the injury increases with dose. No tissue reactions have been observed for absorbed doses below 100 mGy.

The accepted dose-response model for radiation-induced cancer is the linear-non-threshold model (LNT-model) from which several risk-models has been derived (41;42). The LNT-model implies that the smallest dose has the potential to cause a small increase in cancer risk to humans. For ethical reasons, all risk-models are based on epidemiological data from retrospective observational studies. Lifetime risk estimates can be based on both an excess absolute risk (EAR) model and an excess relative risk (ERR) model, the EAR model being recommended by BEIR VII committee. In risk assessment from medical exposure ICRP recommends using appropriate risk values for the individual organ at risk and for the age and sex distribution of the individuals undergoing the medical procedures (41;42).

Radiation detriment from mammography

Acute tissue reactions will not appear from mammography examinations since the doses are well below the observed threshold doses for such reactions.

Within mammography, the organ at risk is the breast. The female breast is identified as a radiosensitive organ by the ICRP and the risk for radiation-induced breast cancer incidence and mortality is highly dependent on age at exposure and assumed linear with the total accumulated absorbed dose to the breast (in AGD), according to the LNT-model (41;42). Lifetime attributable risk (LAR) of radiation-induced breast cancer incidence and mortality in females is shown to increase with decreasing age

at exposure. As a consequence, the estimated risk for radiation-induced breast cancer incidence and mortality from mammography screening is highly dependent on the screening regime, the technology in use, applied examination protocol, age range of the screened population and the screening interval.

No studies with estimated radiation-induced breast cancer incidence and mortality from DBT in mammography screening programmes were found based on a search in the literature. However, many studies with estimated radiation-induced breast cancer incidence and mortality related to different screening regimes using DM were found. Of these studies, only the study performed by Hauge et al. were identified as relevant for this report (43). Hauge et al. estimated the lifetime risk of radiation-induced breast cancer incidence and mortality for the Norwegian Breast Cancer Screening Programme (NBCSP). The risk estimates in this study is based on the risk-model described by Preston et at. (44), which has been adopted by the BEIR VII committee (42) as the most preferred model for estimating radiation-induced breast cancer incidence and mortality. In the NBCSP, women between 50-69 years are screened biennially by two-view DM. Dose data collected by the NBCSP were used in the risk estimates, where the total AGD were found to be 2.5 mGy (range, 0.7-5.7 mGy) to each breast (38). The estimated lifetime risk of radiation-induced breast cancer incidence and mortality per 100,000 women varied between 1.4-36.0 and 0.1-3.1, respectively, depending on the values of different parameters used in the risk-model. The assumed number of lives saved by mammography screening was reported to be approximately 350, based on a mortality reduction of 43% in the NBCSP (13). Lower mortality rates (7-30%) have been reported for the NBCSP in other studies (10). A lower mortality rate will reduce the benefit/risk-ratio estimated by Hauge et al.

The risk estimates obtained in the identified study can be transferred to screening regimes with DBT or DBT in combination with DM, since the risk is assumed linear in the accumulated dose to the breast. Estimated radiation induced breast cancer incidence and mortality for the doses reported from the OTST and STORM-2 trial for DM, DBT and DBT + DM or S2D, based on the risk estimates provided by Hauge et al., are given in Table 8.

Table 8. *Estimated lifetime radiation-induced breast cancer incidence and mortality per 100.000 women for the doses reported by the OTST and STORM-2 trail from biennially screening of women from 50-69 years using DM, DBT and DBT in combination with DM. Numbers are based on the risks estimated by Hauge* et al. *by adjusting the risks according to the dose-ratios (43).*

Study	Total AGD (mGy)	D_{Study}/D_{Hauge}	Incidence	Mortality
Hauge 2014	2.5	1	10.2	0.8
OTST trial				
DM	3.16	1.26	12.9	1.0
DBT	3.90	1.56	15.9	1.2

DBT+DM	7.04	2.82	28.7	2.3
STORM-2 trial				
DM	2.72	1.09	11.1	0.9
DBT	3.74	1.50	15.3	1.2
DBT+DM	6.44	2.58	26.3	2.1

By introducing DBT in combination with DM in the NBCSP, the risk is estimated to increase by a factor of 2.23-2.37 compared to DM. By replacing the DM with S2D images, the risk is estimated to be reduced by 42-45%.

A comprehensive study on radiation-induced breast cancer incidence and mortality from mammography screening was performed by Miglioretti et al. (45). Although this study is not representative for the NBCSP, the results are of general interest when addressing radiation risk from mammography screening. This study included the doses from diagnostic follow-up examinations, additional views and estimated risks from different screening regimes, breast size and breast implants, applying distributions of dose, number of mammographic views and compressed breast size in their risk model. They found that most of the radiation doses were related to the screening examination, only 10% of the mean annual dose was related to diagnostic follow-up examinations. Twenty-one percent of screening examinations used more than four views, something that is often related to thick breasts as dose increases with breast thickness and more images are often required to cover the whole breast. On average, women with large breasts were exposed to 2.3 times higher radiation doses than those with small or average-sized breasts. Breast implants were often associated with additional views, often doubling the dose. Estimated risks related to different screening regimes and breast sizes reported by Miglioretti are summarized in Table 9.

Table 9. *Estimated lifetime radiation-induced breast cancer incidence and mortality for 100.000 women for different screening regimes and breast size (all, average, large) reported by Miglioretti et at (45). The risk estimates include dose from additional examination views and follow-up diagnostic examinations.*

	Incidence			Mortality		
Screening regime	All	Average	Large	All	Average	Large
Annual, 40-74 years	125	113	266	16	15	35
Biennial, 40-74 years	68	61	144	12	11	25
Annual, 50-74 years	49	44	104	7	6	14
Biennial, 50-74 years	27	24	57	4	4	10

The results reported by Miglioretti, show that the lifetime radiation-induced breast cancer incidence and mortality from a screening program will strongly depend on the screening regime applied. The associated risk is also highly related to the breast size of the exposed women.

Radiation risk for staff from mammography

Doses to staff operating the mammography units are negligible as long as they follow the safety requirements given in the national radiation protection regulation (34).

Summary of findings – radiation dose and risk assessment

Introducing the Hologic Selenia Dimensions DBT-system into the Norwegian Breast Cancer Screening Programme (NBCSP) in addition to DM compared to the current practice with DM alone, will cause an increased radiation dose.

Based on the doses reported in the OTST and STORM-2 trial we can estimate that:

- DBT: The dose and risk will increase by 23% to 38%, giving a total AGD of 3.7 to 3.9 mGy and an estimated incidence (per 100,000 women) of radiation-induced breast cancer and mortality of 15 to 16 and 1.2, respectively.
- DBT + DM: The dose and risk will increase by a factor of between 2.23 and 2.37, giving a total AGD of 6.4 to 7.0 mGy and an estimated incidence (per 100,000 women) of radiation-induced breast cancer and mortality women of 26 to 29 and 2.1 to 2.3, respectively.
- DBT + S2D: The dose and risk will be increased by 23% to 38%, but reduced by 42% to 45% compared to DBT + DM, giving the same dose and risk as DBT alone.
- The estimated values for incidence of radiation-induced breast cancer and mortality must be interpreted with caution as there is a high level of uncertainty associated with them. However, the ratio between doses and risks for the different interventions provides valid input to the total risk-benefit evaluation to be done for the screening program.

Cost-effectiveness

Methods for evaluating submitted cost-effectiveness models

Cost-effectiveness analysis

The primary objectives of health economic modeling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard treatment, using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. In order to make comparisons across different types of treatments and multiple potential health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life years (QALYs), a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as

$$Cost_{Intervention} - Cost_{Comparator} \Big/ QALY_{Intervention} - QALY_{Comparator}$$

Evaluating cost-effectiveness models

There is no single correct way to build an economic model to estimate the cost-effectiveness of a specific health initiative. Modeling requires consulting with clinical experts to gain an understanding of normal disease progression, and to determine, based on the research question, the relevant treatment population, relevant comparator; and important health outcomes and adverse events connected to treatment. This information informs the basic model structure, and also determines which clinical effect data is most important to retrieve in the systematic literature search. Once the model structure is in place, the modeler relies on colleagues who perform the systematic search and evidence grading to provide the most reliable risk information for the model, but must also collect all of the relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include enough detail to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying

to answer. Evaluating any given model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable given the research question; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in the model are of adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analysis to determine the degree and source of uncertainty in the model results; and whether the model displays external and internal validity.

Submitted model

Hologic, Inc. has submitted a cost-utility analysis of biennial screening of women aged 50-69 for breast cancer with a combination of digital mammograhpy (DM) and dibtial breast tomosynthesis (DBT) compared to DM alone. It is implied in the submission's budget impact analysis that the DM component in the intervention constitues S2D:

The submitter identified one relevant published cost-effectiveness study from the United States (46).

Table 10. *Identified economic evaluations of DBT+DM vs DM for brest cancer screening*

Study	Model analysis	Population	Incr. QALY	Incr. costs	ICER	Comparison
Lee et al. 2015 (46) United Staates	CUA	Women aged 50-74 screened bi-ennially (12 times).	0,007	0,005	$53 893/ QALY $70 500 per life year gained	Digital mammograph y alone

CUA: Cost-utility analysis; ICER:Incremental cost-effectiveness ratio

Description of the identified economic analysis

The Lee et al. 2015 analysis investigated the cost-utility of DM+DBT versus DM alone in biennial breast cancer screning of women aged 50-75 in the United States (Table 10). It is a discrete event simulation type of health economic model. It is based on a US breast cancer epidemiological model developed by CISNET. The effectiveness data with regard to test performance, however, were derived from an

interim analysis of the Skaane et al. 2013 study (Oslo Tomosynthesis Screening Trial) (3). That is to say, the results from Skaane et al., in which a "marked difference" was seen between DM+DBT and DM alone in terms of sensitivity and specificity, were used in the "best case" analysis of the Lee model. In the base case analysis, the difference in efficacy was adjusted down to a "moderate difference". The base case model results showed a gain of 0,007 and 0,005 QALYs and life-years gained, respectively. The incremental cost per QALY gained was $53,893. An additional 0.5 breast cancer related deaths were averted per 1000 women screened and 405 false-positive caes avoided per 1,000 women after 12 screening rounds. The best case scenario involved an ICER of $26,107 and 1 breast cancer death averted per 1,000 women screened. In the worst case scenario, in which no difference was assumed between the intervention groups, the ICEr was $85,658.

The results from the Lee model in terms of QALYs and life-years gained were used in the submitter's own health economic analysis. The costs, however, were not directly adapted to a Norwegian setting from that model. The reason is that the submitter did not have access to the Lee model. The Lee model and the submitter's costing approach is discussed in some detail below.

Patient population

The patient population in the analysis comprised women between the age of 50 and 70 attending biennial screening in the Norwegian Breast Cancer Screening Programme.

Choice of comparator

The comparator is digital mammography (DM) alone, as currently practised in the Norwegian Breast Cancer Screening Programme.

Type of analysis and decision model

Hologic has submitted a cost-utility analysis (CUA) in which quality-adjusted life year (QALY) results were drawn from the Lee model summarized above (46). In the Lee analysis, two strategies are compared in a discrete event simulation. As Hologic did not have access to the model, the company carried out a cost adaptation to the Norwegian setting not directly linked to the events simulated in the model.

Methods: Intervention and comparator

The discrete event model compared the effects in terms of breast cancer-related mortality reduction and quality-adjusted life years gained for digital mammography (synthetic two dimensional mammography, S2D) + digital breast tomosynthesis vs. digital mammography alone. The model followed a cohort of women between 50 and 70 though repeated screening visits every second year (up to 10 screening events). The time horizon is thus 20 years, while the perspective of the analysis is that of the Norwegian healthcare system. This means that any costs not borne by the healthcare system are excluded, for example patient co-payment or the value of lost working time.

Although the QALY results are derived from the Lee model, the cost approach is not. Rather, separate costing sheets were provided in which Norwegian costs were estimated for each stratey and compared with the model's efficacy results. QALY gains and costs were varied in a number of univariate sensitivity analyses.

Clinical and epidemiological data

As mentioned above, the Lee model was in turn based on a US breast cancer (CISNET) model incorporating outcomes data and overall population mortality. In the Lee model, a hypothetical cohort of women was followed from age 50 to 74 through 12 screening rounds. It was assumed that the additional benefit from the last two screening rounds would be negligible compared to the Norwegian context, where 10 rounds are offered (hence a time horizon of 20 rather than 24 years).

Efficacy

The primary efficacy results were drawn from an interim analysis of the Oslo Tomosynthesis Screening Trial (OTST), Skaane et al. 2013. The results in terms of sensitivity and specificity are shown in Table 11, below. As noted in the summary of the Lee *et al.* 2014 study, these results are adjusted slightly downwards to indicate a moderate difference between the intervention and comparator arms of the model.

Table 11*. Sensitivity and specificity values used in the model (best case shown in brackets)*

	DM	DM/S2D +DBT
Sensitivity	77%	80% (83%)
Specificity	88%	92% (95%)

Recall rates

The submitter presented several studies that have shown a significant decrease in the number of women recalled for additional testing with DM+DBT compared to

DM. Based on these studies, the submitter states that reduction in recall can result in considerable cost savings in US screening scenarios.

In the submitted model it is assumed that screening with DM+DBT will reduce the recall rate by about 0.5% and reduce the total recall rate after 10 screening rounds by about 4% in a US setting. (Table 12).

***Table 12**. Recall rates*

Recall rates	Value
Recall rate DM	3.00%
Recall rate DM+ DBT	2.55%
Screening rounds (Age 50-69)	10
Total recalls DM	26.30%
Total recalls DM+DBT	22.80%
Cost per recall	NOK 2,400
Total recall cost 2D	NOK 643.2
Total cost DBT	NOK 547.2

However, because of a lack of European data in general and information regarding recall related costs in Norway in particular, the submitter assumes that recall-related costs are equal for screening with combined DBT+DM and DM alone in their adapted cost-utility analysis.

Radiologist reading times

The submitter did not explicitly refer to any difference in radiologists' reading (or consensus meeting) time in their economic analysis. It is assumed to be accounted for in the extra reimbursement rates associated with DBT (see costs section). However, in their documentation pack, they state that implementing DBT screening in Norway is likely to increase the reading time for radiologists. Radiologists will have more information to evaluate and require additional time spent in consensus-based arbitration meetings, which includes a minimum of two screening radiologists. According to the study by Skaane et al. 2013, reading times for DM only examinations are approximately 45 seconds compared to 91 seconds with DBT. The submitter points out that the readers will become more experienced (learning curve effect) and then DBT reading times may decrease significantly.

Safety

The submitter did not incorporate radiation exposure in the model. It is assumed that DBT will be used together with S2D in the intervention, which would probably

not increase radiation exposure significantly (see Risks chapter and Safety section in Discussion chapter).

Costs

The costs in the original Lee model are calculated on the basis of a discrete event simulation. The Norwegian costs have not been estimated within the model itself. Instead, the costing follows an approach outlined in a study by Bonafede et al. 2015 (47), another US modeling study. In this study, the addition of DBT to DM results in a shift in the distribution of breast cancer detection towards earlier stages.

Screening costs
The submitter refers to a report by Moger & Kristiansen 2012 (48) when calculating the screening cost related to digital mammography and digital breast tomosynthesis. The cost of DM was set at NOK 745. Because the cost of DBT has yet to be established in Norway, the submitter assumed that costs related to screening would be approximately 40% higher with DBT+DM. The estimate is based on US reimbursement rates. In the costing approach, the submitter evaluated the screening costs over a 20-year time horizon, with ten 2-year screening cycles.

Treatment costs
Breast cancer treatment costs tend to rise with the stage of the disease at diagnosis. Screening may lead to diagnosis at an earlier stage, which can result in cost savings. The submitter has employed a relatively recent Norwegian study by Moger et al. 2016 (49) in combination with the previously mentioned Bonafede study to estimate additional savings following the use of DBT. The Moger study estimated 10-year breast cancer treatment costs by TNM stage as shown in Table 13.

Table 13. *Treatment costs by stage*

	Total costs (NOK)
DCIS	138 761
TNM I	207 788
TNM II	410 375
TNM III	486 897
TNM IV	532 739
Unknown	271 615

*costs converted back to NOK from original Table 4 in Moger et al. using exchange rate EUR= 8,8158 NOK Costs are discounted at 4% p.a. Original table also provides 95% confidence intervals

These costs were weighted by the distribution by stage of cases detected by DM and DM+DBT respectively (see Table 14, below). This table is taken from the Bonafede model (47), which estimated a distribution of detection by stage for DM alone from US observational data. The authors then applied an 18.3% shift in detection across the board from Stage 2 through 4 to Stage 1 to estimate a distribution for DM+DBT.

The estimated shift was based on node status (positive/negative) data from the Skaane et al. 2013 study (OTST). The DCIS/LCIS proportion is estimated to be similar for both strategies.

***Table 14**. Distribution of cases detected by stage and modality*

	DM	DM + DBT
Stage 0 (DCIS/LCIS)	27,90%	27,90%
Stage 1	32,95%	40,12%
Stage 2	27,83%	22,73%
Stage 3	8,58%	7,01%
Stage 4	2,74%	2,24%

Source: Submission attachment/Bonafede et al. 2015 (47)

The submitter, thus, calculated the weighted average treatment costs for the intervention and comparator arms to be:

DM alone	**DM + DBT**
NOK 277 758	NOK 261 408

The weighted treatment costs for DM alone and DM+DBT are multiplied by the breast cancer detection rate per woman screened over 10 rounds (0.08) to obtain the treatment cost per woman screened. These figures are added to the screening costs per woman (Table 15).

***Table 15**. Costs per person screened over 10 rounds*

	Costs, NOK
Total Cost DM	27 971
Total Cost DM+DBT	28 979
Incremental Cost for DBT	1 008

Health related quality of life

The submitter based their health related quality of life (HRQoL) weighting values on the utility values found in the cost-utility model by Lee (46) . The model features age-specific and stage-specific health state utility values for healthy women and women with breast cancer (in stage one to four). The submitted utility values are derived from published EuroQol-5D (EQ-5D) survey results obtained from Lidgren et al. 2007 (50)).

Table 16 presents the quality of life weighting values for healthy women in the four age groups used in the cost-effectiveness model.

***Table 16.** Age specific quality of life weighting values for healthy women*

State of health	Quality of life weight	Source

Healthy (Age 50 to 59)	0.845	(Lidgren 2007, Schousboue 2011)
Healthy (Age 60 to 69)	0.812	(Lidgren 2007, Schousboue 2011)
Healthy (Age 70 to 79)	0.788	(Lidgren 2007, Schousboue 2011)
Healthy (Age 80 +)	0.762	(Lidgren 2007, Schousboue 2011)

HRQoL; Health related quality of life

The model also included reductions for treatment morbidity and loss of utility for patients with breast cancer. The utility values declined in line with the four cancer stages (50;51).

Further, the Lee model included small, transient reductions in utility for women undergoing screening and those undergoing diagnostic work-up after positive screening findings. The utility reduction for screening attendance was given a disutility of 0.006 for one week, and the utility reduction for diagnostic work-up phase was given a disutility of 0.105 for five weeks (52)

The submitter assumed no further reduction in utility for adjunct DBT, since DBT is completed during standard mammographic compression and requires only a few additional seconds.

Our comments on the submitted parameters and input data

Comments on the submitted safety and clinical effectiveness

Efficacy: Ideally, one would have sought to synthesize test performance data to be used in an economic evaluation. However, this can sometimes be challenging for various reasons. Overall, the source of test performance data used by the submitter was considered to be appropriate given that it was a Norwegian – and also relatively recent – study. Compared with the other efficacy results reported (see Table 5) the specificity results seem to be similar. There is however, some uncertainty with regard to the difference in sensitivity between DBT+DM and DM alone.

It seems that the same sensitivity and specificity values are used in every screening round. In the absence of study results reflecting the use of second- and further round use of DBT, this assumption is reasonable. However, it is possible that these values may change over time. A study among women with a high risk of breast cancer showed that sensitivity went down while false positive rates decline over time (53).

Dense breasts: There is uncertainty with regard to whether results can be extrapolated to the non-dense breast population (submitter has reduced the QALY gain to 0.003 in this population in the sensitivity analysis).

Recall rates: It is reasonable to assume that recall rates will decline over time following the introduction of DBT. However, there is some uncertainty regarding the Lee estimate as the baseline recall rate is higher in the US than in Norway due to there only being one reader, structural incentives to conduct extra checks and the screened women may be younger.

Radiologists' reading time: Based on expert opinion (Tron Anders Moger, personal communication), it is considered probable that increased initial reading time and time spent in consensus meetings by radiologists may lead to higher costs. This is because DM would not be replaced by DBT. Both types of examinations should be undertaken on each woman screened (please refer to the clinical results section).

Comments on the costing inputs

Both costs and effects were discounted by 3% except for the treatment costs which were drawn from the Moger costing study, and discounted by 4%. The recommended discount rate for health economic evaluation is slightly higher (4%). However, it is only the screening costs that have been discounted in the adaptation of the model, so the rate is unlikely to have much effect on the costing side.

Screening cots
According to expert opinion (Moger), the DBT is in another tariff group than DM. This results in approximately 40% higher costs for DBT+DM than DM. The 40% added cost for DBT is based on the tariff group price and the deductible.
Based on the tariffs from this year, the cost of DM will be close to NOK 1,000 and for DBT about NOK 1,400.

Treatment costs
As descirbed above, the treatment costs were derived from a recent study by Moger et al. The submitter has used the discounted (4%) value of average 10-year treatment costs per detected cancer patient in their cost calculations. However, as opposed to the screening cost, this cost is not adjusted further. The costing is transparent, but not linked to events or indivudal cost components in the model. It is therefore difficult to explore interlinkages and changes in assumptions. This is a major caveat.

Cost-effectiveness results

The effectiveness results are identical to those estimated in the Lee 2015 model, with 0.007 QALYs and 0.005 life years gained per woman screened over 10 screening rounds. As previously mentioned, the submitter maintains that the benefit accumulated in the last two rounds of the originmal Lee model were neglible and are representative for a Norwegian setting. The total costs per woman screened over the period comprise screening costs and weighted average treament costs as described above. The base case incremental cost effectiveness ratio per QALY gained is NOK 143 960, which is within the range of what is considered to be cost-effective in Norway.

***Table 17**. Base case results presented by the submitter*

Measure	Total costs (NOK)	Total number of life-years	Total number of QALYs	Incremental costs (NOK)	Life years gained	QALY gained	ICER
DM (comparator)	27,971	20.647	16.807	---	---	---	----
DM+BT	28,979	20.652	16.814	1 008	0.005	0.007	143 966

Sensitivity analyses

The submission included univariate sensitivity analyses to account for potential variation of the following variables:

- *Cost of breast tomosynthesis*, where the base case value of NOK 300 was adjusted +/- NOK 200.
- *The incremental QALYs*, where the base case value of 0.007 QALY was adjusted to 0.005 and 0.010 QALY.
- *Cost of cancer treatment:* The cost of treating cancer by stage, where the base case range was NOK 141,600 to NOK 543,870 was adjusted by +/- 25%.

According to the submitted documentation pack the ICER of BT+DM remains below NOK 500,000 across the entire range of variables used in the sensitivity analyses (Table 18). The submitted ICER results were most sensitive to the incremental costs associated with DBT. DM+DBT provided an ICER below NOK 500,000/QALY as long as the incremental cost associated with DBT remained below NOK 623.

***Table 18**. Sensitivity analyses*

Scenario	Total costs (NOK)	Incremental costs (NOK)	QALY gained	ICER
Base case	28 979	1,008	0.007	143 966
DBT cost = NOK 100	27 435	−536	0.007	−76 682
DBT cost = NOK 500	30 523	2 552	0.007	365 515
DBT = 0.010 QALYs gained	28 979	1 008	0.010	100 776
DBT = 0.005 QALYs gained	28 979	1 008	0.005	210 552
Cancer treatment: 25% less than base case	23 751	1 335	0.007	190 681
Cancer treatment: 25% more than base case	34 207	680	0.007	97 252

BT=breast tomosynthesis; ICER=incremental cost effectiveness ratio; NOK=Norwegian krone; QALY=quality-adjusted life-year.

Budget impact analysis

The budget impact analysis covers the first five years after an implementation decision is made. It compares an experimental scenario, in which DBT+S2D is implemented) to a comparator scenario, in which it is not and the current system is maintained. The former involves the gradual phasing in of DBT+S2D screening in Norway.

Both scenarios involve the following cost components:

Cost for additional DBT system purchased
Cost for each screening exam performed
Cost of treatment of detected breast cancer cases

The base case values for these costs in each scenario are listed below.

***Table 19.** Base case unit cost estimates*

Equipment purchase price	1 650 000	2 100 000
Cost per screening exam	745	1045
Average cost of cancer treatment per patient	277 758	261 408

Source: Submission

Main assumptions underlying the analysis:
Currently seven new DM systems are purchased in Norway every year to replace existing ones in a renewal program. A total of 70 mammography systems are installed with an average lifetime of 10 years.

If DBT is adopted, all system purchases would eventually be switched to DBT, but assume that an additional two "DM only" systems would be purchased in year 1 and 2 after implementation.

The total annual cost of equipment purchase for DBT+S2D is thus expected to go down from 18 million NOK in years 1 and 2 to 14.7 million NOK from years 3-5. Screening costs are based on unit costs in the main model cost calculations of screening by 40% (see cost section above). If DBT+S2D were adopted, the proportion of women screened with DBT+S2D is assumed to go up from 15% to 60% over the 5 year period The submitter estimates that approximately 300 000 women are screened for breast cancer each year in Norway.

Adding discounted cancer treatment costs to both scenarios (as calculated in the costing approach above) to screening and equipment purchase costs, the submitter arrives at a total cost difference between the scenarios per year. As seen in the table below, the difference is expected to rise from 10 million in year 1 to 77,5 million in year 5. The rise in later years is due to increased screening with S2D+DBT.

Table 20. *Total budget impact of introducing S2D+DBT over 5 years,* ***NOK million***

Budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5	Total
+ Cost if BT is adopted	856	861	860	863	866	4 306
- Cost without adoption of BT (ie, current situation)	846	846	846	846	846	4 229
Total added cost	10	15	14	17	20	77.5

Various sensitivity analyses were conducted on the budet impact statement, with results ragning from a total cost difference of -53,7 million NOK (subject to a cost dfierence per screening examination of NOk 10) to 165,2 million NOK (cost difference per examination NOK 500).

Comments on the budget impact analysis

Given that the exact of price of the S2D+DBT system has not been established, the budget impact analysis gives a reasonable rough estimate of the expected costs increases following a potential introduction of the new method. However, here too, there is a great deal of uncertainty and the following factors need to be taken into consideration:

- Screening costs may already incorporate apportioned equipment costs, and thus these may be accounted for twice (which implies an overestimation of the actual costs).

- On the other hand, screeening tariffs have increased from 740 to 1000 for DM in 2017, which means that the screening cost difference would have risen to 400. This would increase the potential cost difference.
- The cost of repeat examinations are not incorporated in the budget impact analysis. These would probably have brought the cost difference down somewhat.

Discussion

Clinical effectiveness

We have compared the use of Hologic digital breast tomosynthesis in combination with digital mammography or synthesised digital mammography to digital mammography alone. Our main conclusions are:

- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography decreases or increases **recall rates** compared to digital mammography alone (very low confidence due to conflicting evidence from observational studies)
- The intervention may increase the rate of **screening-detected cancer** (cancer detection rate (CDR) according to all studies (very low confidence due to sparse evidence from one observational study).
- We are uncertain as to whether Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography makes any difference with regard to the detection of **interval cancer** compared to digital mammography alone (very low confidence in the evidence due to sparse evidence from one observational study).
- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography decreases or increases **false positive rates** compared to digital mammography alone (very low confidence due to conflicting evidence from observational studies).
- The intervention may provide similar **sensitivity** rates, but may increase **specificity** rates (low confidence due to evidence from observational studies)
- We are uncertain whether Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography decreases or increases **false negative rates** compared to digital mammography alone (very low confidence due to sparse evidence from one observational study).
- Information on **death** and **quality of life** was not reported.

Uncertainty regarding the effects means that new research may alter our conclusion.

Our findings compared to those of other reviews

We found five recently published review articles (33;54-57). It is not easy to compare and contrast our findings with those of other reviews because the scope of these reviews was not limited to one manufacturer. Also, other reviews have included retrospective studies and most other review authors were funded by the industry.

Houssami and colleagues found evidence from prospective trials, including the OTST, STORM and two other studies, which suggested that tomosynthesis provides enhanced visibility and improves detection of invasive cancers (54). Another review by Coop and colleagues found similar results. This review included OTST, STORM and three other studies, but also found that tomosynthesis increased overall compression time per view by 10 seconds (56).

Pain due to compression of the breast is a major concern because it is thought to be one of the main reasons that women skip mammography. The systematic review conducted by Hodgson and colleagues included studies from Europe and the US, but analyzed them separately due to differences in cancer rates, demographics and screening practices. They found that both cancer detection rates and invasive cancer detection rates improve with tomosynthesis, but the evidence was not statistically significant for non-invasive cancer detection rates. Because of severe heterogeneity, the results for false positive rates and recall rates were not combined in a meta-analysis (33).

A review by Melnikow and colleagues about women with dense breasts found that harm from tomosynthesis could come from additional breast radiation exposure, however use of tomosynthesis may be associated with lower recall rates (57). A rapid review by Houssami and Turner about incremental breast cancer detection in women with dense breast also concluded that there was a significant reduction in recall rates with tomosynthesis (55).

Overall, the reviews varied in terms of scope and inclusion criteria. A commonality was the overall conclusion that there were too few robust and solid trials available to draw firm conclusions about the effectiveness of tomosynthesis. Although one study reported a reduction from 0.7 to 0.5 interval cancers per 100 screened women in the US, there is a need for further evidence for a statistically significant and clinically relevant effect (58).

Comments

Our findings are based on data from the four identified observational studies that compare the use of DBT in addition to DM or S2D with DM alone in large population based screening programs. The studies are all observational studies and according to the GRADE system this means that our confidence to whether the estimates are correct is limited. The risk of bias of the studies according to the QUADAS-2 tool is assessed as low.

The results show that adjunct DBT provides an increased detection rate of invasive breast cancer. The results also indicate that adjunct DBT reduces false positive results and recall rate, but the results are conflicting. One study (PROSPR) finds similar sensitivity, but increased specificity in the DBT+DM arm.

The studies have not looked at outcomes such as breast cancer mortality, quality of life or adverse events. Most studies extended over relatively short time intervals. Only one of the included studies (PROSPR) extends over a longer period (4 years). An increased rate of detection of tumors at an early stage should theoretically lead to a reduced incidence of advanced tumors and higher sensitivity that means less interval cancer. Only one study (PROSPR) considered the interval cancer rate, but only after one year, and found no significant difference. None of the other studies has considered this important outcome. Whether the increased detection is associated with slow-growing tumors that would never give women symptoms during their lifetime unless they had participated in screening, is unclear.

One of the studies was performed in the United States (PROSPR), two in Italy (STORM I and II) and one (OTST) in Norway. Differences in factors such as population age, cultural and socioeconomic background, number of radiologists to analyze the pictures and recall rates, mean that their findings are not necessarily transferable to a Norwegian context and they must be interpreted with caution. For example, the recall rate in recent mammography screening program is significantly lower in Norway than in the US, and the potential for improvement is therefore not the same.

The results and conclusions drawn in this report cannot be generalized to DBT-systems provided by other manufacturers. The radiation dose is highly dependent on the design of the DBT system and different vendors have adopted different solutions. The design will also have impact on the image quality that is directly linked to the clinical outcomes evaluated in this report. In addition, the technology is under continuous development in an attempt to optimize the relationship between dose and image quality.

The risks of false-positive and false-negative mammograms, as well as the risk of overdiagnosis should be taken into account when new technology is evaluated for use in a screening program.

Compared to digital mammography alone, the use of Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography may increase the rate of screen-detected cancer (CDR) according to all studies both for conventional mammography and synthesized 2D mammography. The studies have provided evidence on the first (prevalent) screening round using DM+DBT, which could partly account for the substantial increased cancer detection, compared with standard screening with DM alone. Estimates of screening detection measures for repeat DBT screening of the same populations are needed to quantify the effect of adjunct DBT on both cancer detection and false recalls at repeated screening rounds.

However, none of the studies has randomized patients to receive adjunct DBT. RCTs assessing the impact of adjunct DBT on interval cancer rates as a surrogate for screening benefit would provide critical evidence to underpin future population screening policy and practice. RCTs should be designed to simultaneously address additional evidence gaps such as DBT's incremental cost–effectiveness, and detection measures at repeat screening with adjunct DBT.

Using both DBT and standard DM (dual acquisition) causes an increase in the radiation dose from a radiation protection point of view, DBT-systems with the possibility of generate synthetic 2D images is highly favorable compared to DBT in combination with FFDM, due to its reduction in dose and associated risk. Information on doses should be included in future clinical trials.

Radiation dose and risk assessment

When planning new screening programmes or introducing new technology or techniques in existing screening programmes, it is important to ensure that the clinical benefits outweigh the risks. For screening programmes involving ionizing radiation, the radiation detriment must be incorporated into the total risk-benefit evaluation. Introduction of technologies that increase the dose and risk can only be acceptable if the increase in clinical benefit outweights the risks.

Studies estimating the lifetime radiation-induced cancer incidence and mortality from mammography screening with two-view DM for different screening regimes were identified during the literature search on doses and risks from mammography screening. Doses and risks reported in these studies are summarized in Table 21.

None of the risks estimated in these studies are directly comparable to the risks estimated by Hauge et al. The discrepancies in the reported risks are explained by different screening intervals, age groups and parameter values used in the risk models (dose, DDREF, latency time, follow-up time, etc.).

Table 21. *Estimated lifetime radiation-induced breast cancer incidence and mortality for 100,000 women from mammography screening with two-view FFDM reported in different studies.*

	Total AGD (mGy) from two-view DM	Screening regime (screening interval, age-range in years)	Incidence	Mortality
Hauge 2014 (43)	2.5	Biennially from 50-69	10.2	0.8
Yaffe 2011 (59)	3.7	Annually from 40-55, biennially to 74	86.4	10.6
de Gelder 2011 (60)	1.3*	Biennially from 50-74	7.7	1.6
Miglioretti 2016** (45)	Dose distribution	Biennially from 50-74	27	4
Pauwels 2016 (61)	2.5	Biennially from 50-74	21.2 (2.2‰)	N.A
Hendrick 2010 (62)	3.7	Annually from 50-80	31	10

* In this study the examination technique were two-view the first time and one-view the following examinations.
** Radiation dose from additional views and follow-up diagnostic examinations are included in the risk estimates.

In most of these studies, estimates of risks did not include the additional dose from diagnostic follow-up examinations related to unclear mammographic readings. Technologies that reduce the recall rate and the number of diagnostic follow-ups will also lead to a decrease in the assocoated radiation detriment.

Most studies of mammography screening with DM conclude that the benefits of screening outweight its radiation risks, in particular for women aged 50-69. When introducing DBT in screening the risk/benefit evaluation has to be performed based on the associated dose and clinical outcomes for the different interventions summarized in this report.

From a radiation protection point of view, DBT-systems with the posibility of generating syntetic 2D images (S2D) is highly favorable compared to DBT in combination with DM, due to its reduction in dose and associated risk. Further exploration of whether examination techniques using fewer views are capable of providing comparable clinical outcomes is needed. However, the differences in clinical outcomes need to be considered in the final decision about whether or not to introduce DBT in mammography screening. Information on doses and breast thicknesses should be included in future clinical trials.

Studies reported in the literature demonstrate that the risk of radiation-induced breast cancer due to mammography screening by DBT is small for the women participating in the screening regime used in the Norwegian Breast Cancer

Screening Programme. However, the radiation detriment is only one of the possible harms of mammography screening.

A study performed by Pasicz et al. compared the AGD displayed by a mammography system (DM) with the dose calculated according to the method proposed by Dance (63;64). They concluded that the AGD displayed by the system studied varied significantly compared to the calculated AGD. It is therefore extremely important to verify the dose value reported by the unit as part of the quality control of the equipment to ensure that the doses reported in clinical trials are correct. There is no information about the validity of the doses reported in the OTST and the STORM-2 studies, so caution should be made when comparing and interpreting the reported doses.

According to the Norwegian radiation protection regulation, the decision to introduce DBT in mammography screening must in general be based on the results from a comprehensive HTA to fully adress all the clinical benefits and harms associated with the new technique.

The risk for acute tissue reactions and risks for the staff operating the mammography-systems is negligible.

Cost-effectiveness

The results from the submitter's health economic analysis indicate that adjunct DBT compared to current screening practice could lead to earlier detection of breast cancer and a lower recall rate, though cost reductions emanating from the latter are not actually modelled. The results suggest therefore, that adjunct DBT could be cost-effective if adopted by the Norwegian Breast Cancer Screening Program. However, there are a number of issues that contribute to uncertainty regarding the results. First, the uncertainty described above with regard to the clinical effectiveness, particularly with regard to sensitivity, over repeated screening visits and across different populations (e.g. with respect to breast density). Second, to what extent the potential increase in breast cancer detection leads to increased overdiangosis and unnecessary treatment. Third, since a coherent, adapted health economic model could not be supplied, it is difficult to ascertain the impact of various assumptions in the analysis and assess the total uncertainty regarding the health economic results.

The health economic analysis provided by the submitter suggested that adjunct DBT is cost effective as a consequence of earlier breast cancer detection. However, the total uncertainty associated with the analysis could not be assessed. Coupled with the uncertainty associated with the clinical data at this point, it is as yet not possible to determine whether DBT+DM (S2D) is cost-effective relative to DM alone in Norway.

Resource issues such as the consequences of additional radiologist reading and consensus time as well as data storage should be addressed.

Other studies
There are relatively few economic analyses of DBT, and those which do exist seem to rely on the same source of efficacy data (Skaane 2013). For example, the study cited in the costing approach, Bonafede et al, (47) was a budget impact modeling study comparing DBT+DM with DM alone in a US hypothetical patient population found DBT to be cost saving ($28,53 per woman screened). Test performance seems to be based on Skaane et al. 2013. (3). However, screening on an annual basis and population age distribution may be wider than in Norway. Mille et al. 2017 (65) was a similar budget impact model which predicted an annual saving of $8,14 per Medicaid patient per year I the US as a result of adding DBT to DM in annual breast cancer screening. In this study too, Lower recall rates and earlier detection were the main drivers with regard to cost savings.

Challenges with respect to the STA format

Hologic is the only manufacturer that has submitted a documentation pack for assessment of DBT for screening use. The submitter could not provide direct access to the health economic model within the time frame of this single-technology assessment. Even if model access had been possible, a report in the STA format could not have appropriately answered the question of whether DBT in general is an effective, safe and cost-effective screening method for breast cancer. First, the evidence related to a single supplier may be too limited. Second, the model results do not say anything about which – if any – of the suppliers' equipment is the most cost-effective.

The results and conclusions drawn in this report cannot be generalized to DBT-systems provided by other manufacturers.

Conclusion

There is too little evidence to conclude regarding the effects of the use of Hologic digital breast tomosynthesis in combination with digital mammography or synthesized digital mammography compared to digital mammography alone for the outcomes assessed in our report (recall rates, cancer detection rate, interval cancer rate, false positive and false negative rate, sensitivity, specificity, mortality and quality of life).

Preparation of a full health technology assessment should be considered when sufficient evidence is available.

References

1. Hologic Inc. Breast tomosynthesis: A review of clinical and economic evidence for the Hologic 3D Mammography Selenia® Dimensions® System. [unpublished]. 2016.
2. CADTH. Tomosynthesis (3D Mammography) for Breast Cancer Screening. Health CAfDaTi; 2015.
3. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology 2013;267(1):47-56.
4. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fanto C, Ostillio L, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. Lancet Oncol 2016;17(8):1105-13.
5. Nasjonal rådgivningsgruppe for Mammografiprogrammet. Tomosyntese i mammografiscreening. [Norwegian]. Oslo: Cancer Registry of Norway; 2015.
6. Cancer Registry of Norway. Cancer in Norway 2015: Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2016.
7. Helsedirektoratet. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av pasienter med brystkreft Oslo: Helsedirektoratet; 2016. Nasjonale faglige retningslinjer. IS-2440.
8. Norwegian Institute of Public Health. Dødsårsaksregisterets statistikkbank. [Cause of Death Registry]Oslo: Norwegian Institute of Public Health [updated 02.11.2016; cited]. Available from: http://statistikkbank.fhi.no/dar/
9. WHO. Screening for various cancers: World Health Organization [cited]. Available from: http://www.who.int/cancer/detection/variouscancer/en/
10. The Research Council of Norway. Research-based evaluation of the Norwegian Breast Cancer Screening Program: Final report. Lysaker: The Research Council of Norway; 2015.
11. Hoff SR, Samset JH, Abrahamsen AL, Vigeland E, Klepp O, Hofvind S. Missed and true interval and screen-detected breast cancers in a population based screening program. Acad Radiol 2011;18(4):454-60.
12. Cancer Registry of Norway. Breast Cancer Screening Programme[cited 17. March]. Available from: https://www.kreftregisteret.no/screening/Mammografiprogrammet/
13. Hofvind S, Ursin G, Tretli S, Sebuodegard S, Moller B. Breast cancer mortality in participants of the Norwegian Breast Cancer Screening Program. Cancer 2013;119(17):3106-12.
14. Cancer Registry of Norway. Mammografiprogrammet: Resultater fra prosessindikatorer 2006-2013/14. [Norwegian]. Oslo: Cancer Registry of Norway; 2015.

15. Sebuodegard S, Sagstad S, Hofvind S. Oppmøte i Mammografiprogrammet. [Norwegian]. Tidsskr Nor Laegeforen 2016;136(17):1448-51.
16. Hofvind S, Skaane P, Elmore JG, Sebuodegard S, Hoff SR, Lee CI. Mammographic performance in a population-based screening program: before, during, and after the transition from screen-film to full-field digital mammography. Radiology 2014;272(1):52-62.
17. Tingberg A, Zackrisson S. Digital mammography and tomosynthesis for breast cancer diagnosis. Expert Opin Med Diagn 2011;5(6):517-26.
18. Houssami N, Skaane P. Overview of the evidence on digital breast tomosynthesis in breast cancer detection. Breast 2013;22(2):101-8.
19. Houssami N, Lang K, Bernardi D, Tagliafico A, Zackrisson S, Skaane P. Digital breast tomosynthesis (3D-mammography) screening: A pictorial review of screen-detected cancers and false recalls attributed to tomosynthesis in prospective screening trials. Breast (Edinburgh, Scotland) 2016;26:119-34.
20. Friedewald SM. Breast tomosynthesis: Practical considerations. Radiol Clin North Am 2017;55(3):493-502.
21. Skaane P, Bandos AI, Eben EB, Jebsen IN, Krager M, Haakenaasen U, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology 2014;271(3):655-63.
22. Tryggvadottir L, Gislum M, Bray F, Klint A, Hakulinen T, Storm HH, et al. Trends in the survival of patients diagnosed with breast cancer in the Nordic countries 1964-2003 followed up to the end of 2006. Acta Oncol 2010;49(5):624-31.
23. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. Breast-cancer screening: Viewpoint of the IARC Working Group. N Engl J Med 2015;372(24):2353-8.
24. Lauby-Secretan B, Scoccianti C, Loomis D, Bianchini F, Benbrahim-Tallaa L, Bouvard V, et al. The IARC handbooks of cancer prevention: Volume 15: Breast cancer screening. [poster]. N Engl J Med 2015;372(24):2353-8 - special report.
25. Conant EF, Beaber EF, Sprague BL, Herschorn SD, Weaver DL, Onega T, et al. Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: a cohort study within the PROSPR consortium. Breast Cancer Res Treat 2016;156(1):109-16.
26. McDonald ES, Oustimov A, Weinstein SP, Synnestvedt MB, Schnall M, Conant EF. Effectiveness of digital breast tomosynthesis compared with digital mammography: Outcomes analysis from 3 years of breast cancer Screening. JAMA Oncol 2016;2(6):737-43.
27. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration. Eur Radiol 2013;23(8):2061-71.
28. Bernardi D, Caumo F, Macaskill P, Ciatto S, Pellegrini M, Brunelli S, et al. Effect of integrating 3D-mammography (digital breast tomosynthesis) with 2D-mammography on radiologists' true-positive and false-positive detection in a population breast screening trial. Eur J Cancer 2014;50(7):1232-8.
29. Caumo F, Bernardi D, Ciatto S, Macaskill P, Pellegrini M, Brunelli S, et al. Incremental effect from integrating 3D-mammography (tomosynthesis) with 2D-mammography: Increased breast cancer detection evident for screening centres in a population-based trial. Breast 2014;23(1):76-80.
30. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population

breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol 2013;14(7):583-9.
31. Houssami N, Macaskill P, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading--evidence to guide future screening strategies. Eur J Cancer 2014;50(10):1799-807.
32. McCarthy AM, Kontos D, Synnestvedt M, Tan KS, Heitjan DF, Schnall M, et al. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. J Natl Cancer Inst 2014;106(11):dju316.
33. Hodgson R, Heywang-Kobrunner SH, Harvey SC, Edwards M, Shaikh J, Arber M, et al. Systematic review of 3D mammography for breast cancer screening. Breast 2016;27:52-61.
34. Forskrift om strålevern og bruk av stråling (strålevernforskriften). FOR-2016-12-16-1659.
35. COUNCIL DIRECTIVE 2013/59/EURATOM of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. COUNCIL DIRECTIVE 2013/59/EURATOM.
36. Sechopoulos I. A review of breast tomosynthesis: Part I. The image acquisition process. Med Phys 2013;40(1):014301.
37. Svahn TM, Houssami N, Sechopoulos I, Mattsson S. Review of radiation dose estimates in digital breast tomosynthesis relative to those in two-view full-field digital mammography. Breast 2015;24(2):93-9.
38. Hauge IH, Pedersen K, Sanderud A, Hofvind S, Olerud HM. Patient doses from screen-film and full-field digital mammography in a population-based screening programme. Radiat Prot Dosimetry 2012;148(1):65-73.
39. Maldera A, De Marco P, Colombo PE, Origgi D, Torresin A. Digital breast tomosynthesis: Dose and image quality assessment. Phys Med 2017;33:56-67.
40. Rodriguez-Ruiz A, Castillo M, Garayoa J, Chevalier M. Evaluation of the technical performance of three different commercial digital breast tomosynthesis systems in the clinical environment. Phys Med 2016;32(6):767-77.
41. The 2007 Recommendations of the International Commission on Radiological Protection. (ICRP Publication 103). Ann ICRP 2007;37(2-4).
42. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects, Research Division on Earth and Life Studies, National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation : BEIR VII, Phase 2. Washington DC: National Academies Press; 2006.
43. Hauge IH, Pedersen K, Olerud HM, Hole EO, Hofvind S. The risk of radiation-induced breast cancers due to biennial mammographic screening in women aged 50-69 years is minimal. Acta Radiol 2014;55(10):1174-9.
44. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD, Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 2002;158(2):220-35.
45. Miglioretti DL, Lange J, van den Broek JJ, Lee CI, van Ravesteyn NT, Ritley D, et al. Radiation-induced breast cancer incidence and mortality from digital mammography screening: A modeling study. Ann Intern Med 2016;164(4):205-14.
46. Lee CI, Cevik M, Alagoz O, Sprague BL, Tosteson AN, Miglioretti DL, et al. Comparative effectiveness of combined digital mammography and

tomosynthesis screening for women with dense breasts. Radiology 2015;274(3):772-80.
47. Bonafede MM, Kalra VB, Miller JD, Fajardo LL. Value analysis of digital breast tomosynthesis for breast cancer screening in a commercially-insured US population. ClinicoEconomics and outcomes research : CEOR 2015;7:53-63.
48. Moger TAKIS. Direct and indirect costs of the Norwegian Breast Cancer Screening Program. Institute of Health and Society, Department of Health Management and Health Economics, University of Oslo
Department of Health Management and Health Economics, University of Oslo
P.O. Box 1089 Blindern, NO-0317 Oslo, Norway; 2012.
49. Moger TA, Bjornelv GM, Aas E. Expected 10-year treatment cost of breast cancer detected within and outside a public screening program in Norway. The European journal of health economics : HEPAC : health economics in prevention and care 2016;17(6):745-54.
50. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Qual Life Res 2007;16(6):1073-81.
51. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Ann Intern Med 2011;155(1):10-20.
52. de Haes JC, de Koning HJ, van Oortmarssen GJ, van Agt HM, de Bruyn AE, van Der Maas PJ. The impact of a breast cancer screening programme on quality-adjusted life-years. Int J Cancer 1991;49(4):538-44.
53. Chamberlain J, Clifford RE, Nathan BE, Price JL, Burn I. Repeated screening for breast cancer. J Epidemiol Community Health 1984;38(1):54-7.
54. Houssami N, Lang K, Bernardi D, Tagliafico A, Zackrisson S, Skaane P. Digital breast tomosynthesis (3D-mammography) screening: A pictorial review of screen-detected cancers and false recalls attributed to tomosynthesis in prospective screening trials. Breast 2016;26:119-34.
55. Houssami N, Turner RM. Rapid review: Estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts. Breast 2016;30:141-5.
56. Coop P, Cowling C, Lawson C. Tomosynthesis as a screening tool for breast cancer: A systematic review. Radiography 2016;22(3):e190-e5.
57. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: A systematic review for the U.S. Preventive services task force. Ann Intern Med 2016;164(4):268-78.
58. Sardanelli F, Fallenberg EM, Clauser P, Trimboli RM, Camps-Herrero J, Helbich TH, et al. Mammography: an update of the EUSOBI recommendations on information for women. Insights Imaging 2017;8(1):11-8.
59. Yaffe MJ, Mainprize JG. Risk of radiation-induced breast cancer from mammographic screening. Radiology 2011;258(1):98-105.
60. de Gelder R, Draisma G, Heijnsdijk EA, de Koning HJ. Population-based mammography screening below age 50: balancing radiation-induced vs prevented breast cancer deaths. Br J Cancer 2011;104(7):1214-20.
61. Pauwels EK, Foray N, Bourguignon MH. Breast cancer induced by x-ray mammography screening? A review based on recent understanding of low-dose radiobiology. Med Princ Pract 2016;25(2):101-9.
62. Hendrick RE. Radiation doses and cancer risks from breast imaging studies. Radiology 2010;257(1):246-53.
63. Dance DR, Skinner CL, Young KC, Beckett JR, Kotre CJ. Additional factors for the estimation of mean glandular breast dose using the UK mammography dosimetry protocol. Phys Med Biol 2000;45(11):3225-40.

64. Pasicz K, Fabiszewska E, Grabska I, Skrzynski W. Mean glandular doses in mammography: a comparison of values displayed by a mammography unit with in-house values, both using the method proposed by Dance. J Radiol Prot 2016;36(3):709-15.
65. Miller JD, Bonafede MM, Herschorn SD, Pohlman SK, Troeger KA, Fajardo LL. Value Analysis of Digital Breast Tomosynthesis for Breast Cancer Screening in a US Medicaid Population. J Am Coll Radiol 2017.

Appendix

Appendix 1 List of ongoing studies reported by submitter

In-progress clinical trials of BT in the EU and US

Clinical Trial ID	Title of Trial	Status
NCT00721435	Combined digital x-ray and ultrasound technique for improved detection and characterization of breast lesions	Active, not recruiting
NCT00723541	Tomosynthesis mammography: computer-aided analysis of breast lesions	Recruiting
NCT00971087	Multicenter Hologic tomosynthesis study	Unknown
NCT01060085	Digital breast tomosynthesis versus contrast-enhanced magnetic resonance imaging (MRI) for breast cancer staging	Active, not recruiting
NCT01086241	A study to determine patient benefit of tomosynthesis in screening mammography	Unknown
NCT01091545	Malmö breast tomosynthesis screening trial	Active, not recruiting
NCT01106911	Assessment of digital breast tomosynthesis (DBT) in the screening environment: a prospective study	Unknown
NCT01236781	Comparison of full-field digital mammography with digital breast tomography for screening call-back rates	Unknown
NCT01241981	Digital breast tomosynthesis in younger symptomatic women	Unknown
NCT01248546	Digital breast tomosynthesis in the Oslo mammography screening program	Unknown
NCT01524029	Digital breast tomosynthesis versus digital mammography: a national multicenter trial	Unknown
NCT01569802	A comparison of recall rates between conventional 2D mammography and 2D plus 3D (tomosynthesis) mammography in a screening population	Unknown
NCT01612650	Assessment of substitution of focused cliches and ultrasound for tomosynthesis	Recruiting
NCT01669148	Breast cancer detection: comparison of breast tomosynthesis and conventional mammography	Unknown
NCT01716247	Comparison of contrast-enhanced mammography to breast MRI in screening patients at increased risk for breast cancer	Active, not recruiting
NCT01773850	Comparison of stationary breast tomosynthesis and 2D digital mammography in patients with known breast lesions	Recruiting
NCT01807754	Simulated screening study of combined digital X-ray, ultrasound and photoacoustic breast imaging	Recruiting
NCT01852032	Computed tomography versus standard 2D mammography	Ongoing,

Clinical Trial ID	Title of Trial	Status
	versus 3D tomosynthesis	not recruiting
NCT01881880	Value of tomosynthesis in breast lesion characterization and breast cancer staging	Unknown
NCT02008032	Comparison of stationary breast tomosynthesis and 2D digital mammography in patients with breast augmentation	Recruiting
NCT02033486	Digital breast tomosynthesis-guided tomographic optical breast imaging (TOBI)	Recruiting
NCT02066142	Tomosynthesis (TS) versus ultrasonography (U/S) in screening women with dense breast	Recruiting
NCT02096185	Is any additional information gained regarding lesion to margin measurement using 3D tomosynthesis imaging versus 2D conventional digital imaging when imaging specimens of breast tissue removed at therapeutic surgery?	Enrolling by invitation
NCT02156258	Acquisition of digital mammography and breast images for clinical evaluation of Fujifilm Digital breast tomosynthesis	Active, not recruiting
NCT02174406	Clinical utility of whole breast screening ultrasound in patients undergoing digital breast tomosynthesis	Recruiting
NCT02209129	3D digital breast tomosynthesis versus 2D digital mammography in the clinical evaluation of women at high risk for breast cancer	Recruiting
NCT02306265	Assessment of diagnostic accuracy and performance of digital breast tomosynthesis compared to mammography (ADAPT Trial) ADAPT-SCR: recruitment plan for asymptomatic women undergoing screening mammography	Active, not recruiting
NCT02324205	Assessment of diagnostic accuracy and performance of digital breast tomosynthesis compared to mammography (ADAPT Trial) ADAPT-BX: recruitment plan for initially asymptomatic women referred for breast biopsy	Recruiting
NCT02386176	Assessment of automated breast ultrasound	Recruiting
NCT02540083	Assessment of diagnostic accuracy and performance of digital breast tomosynthesis compared to mammography (ADAPT-ENRICH)	Recruiting
NCT02590315	Tomosynthesis versus digital mammography in a population-based screening programme (ProteusDonna)	Recruiting
NCT02616432	Tomosynthesis mammography imaging screening trial	Recruiting
NCT02643966	Assessment of periodic screening of women with denser breast using WBUS and DBT (DBTUST)	Recruiting

2D=2-dimensional; 3D=3-dimensional; BT=breast tomosynthesis; DBT=digital breast tomosynthesis; EU=European Union; GE=General Electric; ID=identification; MRI=magnetic resonance imaging; NCT=national clinical trial; TOBI=tomographic optical breast imaging; TS=tomosynthesis; US=United States; U/S=ultrasonography; WBUS=whole breast ultrasound.

SOURCES: ClinicalTrials.gov; ClinicalTrialsRegister.eu.

Appendix 2 Norwegian Institute of Public Health's search strategies

Updated literature search: Search log and strategies
Search period: 2016-2017
Search date: 14/02/2017
Records retrieved from databases and exported to EndNote (total): 1663
Records of ongoing trials to be screened by project team: 59

Database	Retrieved records/ Comment
MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	250
Embase 1974 to 2017 February 13 (OvidSP)	521
Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2017 (Wiley)	0
Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2017 (Wiley)	18
Health Technology Assessment Database (Wiley)	0
Web of Science Core Collection	301
LILACS	223
Clinical Trials	20 (not deduplicated; not imported to EndNote)
International Clincial Trials Registry Platform (ICTRP)	39 (not deduplicated; not imported to EndNote)
NICE	To be screened by project group
NHS Breast Screening Programme webpages	To be screened by project group
PubMed (National Library of Medicine) Subset: pubmednotmedline	311

MEDLINE

1	(Selenia$ Dimensions$ or Mammomat$ or Novation$ or Inspiration 3D$ or Inspiration Prime$ or SenoClaire$ or Seno Claire$ or Senograph$ or Aspire Innovality$ or Aspire F or Aspire S or Cristalle$ or Diagnost or Phillips Microdose$ or Giotto$ or Clarity 3d or Clarity 2d or Nuance Excel).ti,ab,kf.	320
2	((3d or 3-d or three dimension$ or 3 dimension$) adj4 mammogra$).ti,ab,kf.	126
3	((3d or 3-d or three dimension$ or 3 dimension$) adj4 (breast$ or mammar$)).ti,ab,kf.	1199
4	exp Mammography/ and exp Imaging, Three-Dimensional/	403
5	(tomosynth$ or tomo-synth$ or DBT).ti,ab,kf.	2606
6	(Hologic$ or Siemens$ or GE Medical$ or Fujifilm$ or Phillips$ or Giotto$ or PlanMed$).ti,ab,kf,in.	22739
7	(breast$ or mammar$ or mammogra$).ti,ab,kf,jw.	431527
8	exp breast neoplasms/	251927
9	exp Breast/ and exp Neoplasms/	23564
10	exp mammography/	26709
11	5 or 6	25277
12	or/7-10	463408
13	11 and 12	1459
14	1 or 2 or 3 or 4 or 13	3001
15	exp animals/ not humans/	4325671
16	14 not 15	2918
17	(201607* or 201608* or 201609*or 201610* or 201611* or 201612* or 2017*).ed,ep,yr.	838430
18	16 and 17	264
19	remove duplicates from 18	250

Embase

1	(Selenia$ Dimensions$ or Mammomat$ or Novation$ or Inspiration 3D$ or Inspiration Prime$ or SenoClaire$ or Seno Claire$ or Senograph$ or Aspire Innovality$ or Aspire F or Aspire S or Cristalle$ or Diagnost or Phillips Microdose$ or Giotto$ or Clarity 3d or Clarity 2d or Nuance Excel).ti,ab,kw.	415
2	((3d or 3-d or three dimension$ or 3 dimension$) adj4 mammogra$).ti,ab,kw.	153
3	((3d or 3-d or three dimension$ or 3 dimension$) adj4 (breast$ or mammar$)).ti,ab,kw.	1656
4	exp mammography/ and three dimensional imaging/	699
5	(tomosynth$ or tomo-synth$ or DBT).ti,ab,kw.	3373

6	(Hologic$ or Siemens$ or GE Medical$ or Fujifilm$ or Phillips$ or Giotto$ or PlanMed$).ti,ab,kw.	22581
7	(breast$ or mammar$ or mammogra$).ti,ab,kw,jx.	553951
8	exp breast tumor/	454847
9	exp breast/ and exp neoplasm/	109727
10	exp mammography/	49209
11	5 or 6	25885
12	or/7-10	636154
13	11 and 12	1584
14	1 or 2 or 3 or 4 or 13	3859
15	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5405399
16	14 not 15	3740
17	("201628" or "201629" or 20163* or 20164* or 20165* or 2017*).em,yr.	2250555
18	16 and 17	533
19	remove duplicates from 18	521

Cochrane Library: Cochrane Reviews

#1	(Selenia* next Dimensions* or Mammomat* or Novation* or Inspiration next 3D* or Inspiration next Prime* or SenoClaire* or Seno next Claire* or Senograph* or Aspire next Innovality* or "Aspire F" or "Aspire S" or Cristalle* or Diagnost or Phillips next Microdose* or Giotto* or "Clarity 3d" or "Clarity 2d" or "Nuance Excel"):ti,ab,kw	10
#2	((3d or 3-d or three next dimension* or 3 next dimension*) near/4 mammogra*):ti,ab,kw	9
#3	((3d or 3-d or three next dimension* or 3 next dimension*) near/4 (breast* or mammar*)):ti,ab,kw	52
#4	[mh Mammography] and [mh "Imaging, Three-Dimensional"]	8
#5	(tomosynth* or tomo-synth* or DBT):ti,ab,kw	169
#6	(Hologic* or Siemens* or GE next Medical* or Fujifilm* or Phillips* or Giotto* or PlanMed*):ti,ab,kw	543
#7	(breast* or mammar* or mammogra*):ti,ab,kw	30305
#8	[mh "Breast Neoplasms"]	10051
#9	[mh Breast] and [mh Neoplasms]	320
#10	[mh Mammography]	1038

#11	#5 or #6	707
#12	#7 or #8 or #9 or #10	30305
#13	#11 and #12	50
#14	#1 or #2 or #3 or #4 or #13 Publication Year from 2016, in Cochrane Reviews (Reviews and Protocols) (Word variations have been searched)	0

Cochrane Library: Trials

#1	(Selenia* next Dimensions* or Mammomat* or Novation* or Inspiration next 3D* or Inspiration next Prime* or SenoClaire* or Seno next Claire* or Senograph* or Aspire next Innovality* or "Aspire F" or "Aspire S" or Cristalle* or Diagnost or Phillips next Microdose* or Giotto* or "Clarity 3d" or "Clarity 2d" or "Nuance Excel")	20
#2	((3d or 3-d or three next dimension* or 3 next dimension*) near/4 mammogra*)	9
#3	((3d or 3-d or three next dimension* or 3 next dimension*) near/4 (breast* or mammar*))	51
#4	[mh Mammography] and [mh "Imaging, Three-Dimensional"]	8
#5	(tomosynth* or tomo-synth* or DBT)	196
#6	(Hologic* or Siemens* or GE next Medical* or Fujifilm* or Phillips* or Giotto* or PlanMed*)	3854
#7	(breast* or mammar* or mammogra*)	33122
#8	[mh "Breast Neoplasms"]	10051
#9	[mh Breast] and [mh Neoplasms]	320
#10	[mh Mammography]	1038
#11	#5 or #6	4043
#12	#7 or #8 or #9 or #10	33122
#13	#11 and #12	261
#14	#1 or #2 or #3 or #4 or #13 Publication Year from 2016 to 2017, in Trials (Word variations have been searched)	18

Cochrane Library: Technology Assessments

#1	(Selenia* next Dimensions* or Mammomat* or Novation* or Inspiration next 3D* or Inspiration next Prime* or SenoClaire* or Seno next Claire* or Senograph* or Aspire next Innovality* or "Aspire F" or "Aspire S" or Cristalle* or Diagnost or Phillips next Microdose* or Giotto* or "Clarity 3d" or "Clarity 2d" or "Nuance Excel")	20
#2	((3d or 3-d or three next dimension* or 3 next dimension*) near/4 mammogra*)	9

#3	((3d or 3-d or three next dimension* or 3 next dimension*) near/4 (breast* or mammar*))	51
#4	[mh Mammography] and [mh "Imaging, Three-Dimensional"]	8
#5	(tomosynth* or tomo-synth* or DBT)	196
#6	(Hologic* or Siemens* or GE next Medical* or Fujifilm* or Phillips* or Giotto* or PlanMed*)	3854
#7	(breast* or mammar* or mammogra*)	33122
#8	[mh "Breast Neoplasms"]	10051
#9	[mh Breast] and [mh Neoplasms]	320
#10	[mh Mammography]	1038
#11	#5 or #6	4043
#12	#7 or #8 or #9 or #10	33122
#13	#11 and #12	261
#14	#1 or #2 or #3 or #4 or #13 Publication Year from 2016 to 2017, in Technology Assessments (Word variations have been searched)	0

Web of Science

#1	TS=("Selenia* Dimensions*" or Mammomat* or Novation* or "Inspiration 3D*" or "Inspiration Prime*" or SenoClaire* or "Seno Claire*" or Senograph* or "Aspire Innovality*" or "Aspire F" or "Aspire S" or Cristalle* or "Diagnost" or "Phillips Microdose*" or "Clarity 3d" or "Clarity 2d" or "Nuance Excel")	250
#2	TS=(Giotto* and (breast* or mammar* or mammogra* or tomo* or "DBT"))	8
#3	TS=(("3d" or "3-d" or "three dimension*" or "3 dimension*") near/3 mammogra*)	126
#4	TS=(("3d" or "3-d" or "three dimension*" or "3 dimension*") near/3 (breast* or mammar*))	1271
#5	TS=(tomosynth* or tomo-synth* or "DBT")	4983
#6	TS=(Hologic* or Siemens* or "GE Medical*" or Fujifilm* or Phillips* or PlanMed*)	15227
#7	TS=(breast* or mammar* or mammogra*)	573636
#8	#6 OR #5	20167
#9	#8 AND #7	1292
#10	#9 OR #4 OR #3 OR #2 OR #1	2688
#11	TI=("rat" or "rats" or "rodent" or "rodents" or "mouse" or "mice" or "murine" or "hamster" or "hamsters" or "gerbil" or "gerbils" or "ani-	1595384

	mal" or "animals" or "dogs" or "dog" or "canine" or "pig" or "pigs" or "cats" or "bovine" or "cow" or "cows" or "cattle" or "sheep" or "horse" or "horses" or "equine" or "ovine" or "porcine" or "monkey" or "monkeys" or "primate" or "primates" or "rhesus macaque" or "rhesus macaques" or "rabbit" or "rabbits") not TS=human*	
#12	#10 not #11 Timespan=2016-2017	340

LILACS

Search 1:
(TI:"Selenia Dimensions" OR TI:Mammomat$ OR TI:Novation$ OR TI:"Inspiration 3D" OR TI:"Inspiration Prime" OR TI:SenoClaire$ OR TI:"Seno Claire" OR TI:Senograph$ OR TI:"Aspire Innovality" OR TI:"Aspire F" OR TI:"Aspire S" OR TI:Cristalle$ OR TI:Diagnost OR TI:"Phillips Microdose" OR TI:Giotto$ OR TI:"Clarity 3d" OR TI:"Clarity 2d" OR TI:"Nuance Excel" OR AB:"Selenia Dimensions" OR AB:Mammomat$ OR AB:Novation$ OR AB:"Inspiration 3D" OR AB:"Inspiration Prime" OR AB:SenoClaire$ OR AB:"Seno Claire" OR AB:Senograph$ OR AB:"Aspire Innovality" OR AB:"Aspire F" OR AB:"Aspire S" OR AB:Cristalle$ OR AB:Diagnost OR AB:"Phillips Microdose" OR AB:Giotto$ OR AB:"Clarity 3d" OR AB:"Clarity 2d" OR AB:"Nuance Excel")
Filter: 2016
Records retrieved: 0

Search 2:
(TI:3d OR TI:"3-d" OR TI:"three dimension" OR TI:"three dimensions" OR TI:"three dimensional" OR TI:"3 dimension" OR TI:"3 dimensions" OR TI:"3 dimensional" OR AB:3d OR AB:"3-d" OR AB:"three dimension" OR AB:"three dimensions" OR AB:"three dimensional" OR AB:"3 dimension" OR AB:"3 dimensions" OR AB:"3 dimensional") AND (TI:mammogra$ OR TI:breast$ OR TI:mammar$ OR AB:mammogra$ OR AB:breast$ OR AB:mammar$)

Filter: 2016
Records retrieved: 2

Search 3:
(TI:tomosynth$ OR TI:"tomo-synthesis" OR TI:"tomo-synthesise" OR TI:"tomo-synthesize" OR TI:DBT OR TI:Hologic$ OR TI:Siemens$ OR TI:"GE Medical" OR TI:Fujifilm$ OR TI:Phillips$ OR TI:PlanMed$ OR AB:tomosynth$ OR AB:"tomo-synthesis" OR AB:"tomo-synthesise" OR AB:"tomo-synthesize" OR AB:DBT OR AB:Hologic$ OR AB:Siemens$ OR AB: "GE Medical" OR AB:Fujifilm$ OR AB:Phillips$ OR AB:PlanMed$) AND (TI:breast$ OR TI:mammar$ OR TI:mammogra$ OR AB:breast$ OR AB:mammar$ OR AB:mammogra$ OR MH:"Breast Neoplasms" OR MH:"Breast Neoplasms, Male" OR MH:"Carcinoma, Ductal, Breast" OR MH:"Hereditary Breast and Ovarian Cancer Syndrome" OR MH:"Inflammatory Breast Neoplasms" OR MH:"Triple Negative Breast Neoplasms" OR MH:Mammography OR MH:Xeromammography)
Filter: 2016

Records retrieved: 221

Clinical Trials

Checked that adding more synonyms from original search does not retrieve more records.

Search 1:
(Selenia Dimensions OR Mammomat OR Novation OR Inspiration 3D OR Inspiration Prime OR SenoClaire OR Seno Claire OR Senograph OR Aspire Innovality OR Aspire F OR Aspire S OR Cristalle OR Diagnost OR Phillips Microdose OR Giotto)

Studies received from 07/11/2016 to 02/14/2017

Records retrieved: 6

Clarity 3d OR Clarity 2d OR Nuance Excel OR ((tomosynthesis OR DBT OR Hologic OR Siemens OR GE Medical OR Fujifilm OR Phillips OR PlanMed OR 3 dimensional OR 3 dimensions) AND (mammography OR mammographic OR breast))

Studies received from 07/11/2016 to 02/14/2017

Records retrieved: 14

ICTRP

Search 1:
Selenia Dimensions* OR Mammomat* OR Novation* OR Inspiration 3D* OR Inspiration Prime* OR SenoClaire* OR Seno Claire* OR Senograph* OR Aspire Innovality* OR Cristalle* OR Diagnost OR Phillips Microdose* OR Giotto* OR Clarity 3d OR Clarity 2d OR Nuance Excel
Records retrieved: 6
Date of Registration after 07/11/2016: 0

Search 2:
breast AND aspire OR mammogra* AND aspire OR mammar* AND aspire
Records retrieved: 1
Date of Registration after 07/11/2016: 0

Search 3:
tomosynth* AND mammogra* OR tomo-synth* AND mammogra* OR DBT AND mammogra* OR Hologic AND mammogra* OR Siemens AND mammogra* OR GE Medical AND mammogra* OR Fujifilm AND mammogra* OR Phillips AND mammogra* OR PlanMed AND mammogra* OR tomosynth* AND breast* OR tomo-synth* AND breast* OR DBT AND breast* OR Hologic AND breast* OR Siemens AND breast* OR GE Medical AND breast* OR Fujifilm AND breast* OR Phillips AND breast* OR PlanMed AND breast* OR tomosynth* AND mammar* OR tomo-synth* AND mammar* OR DBT AND mammar* OR Hologic AND mammar* OR Siemens AND mammar* OR GE Medical AND mammar* OR Fujifilm AND mammar* OR Phillips AND mammar* OR PlanMed AND mammar*

Records retrieved: 75
Date of Registration after 07/11/2016: 5

Search 4:
3d AND mammogra* OR 3-d AND mammogra* OR three dimension* AND mammogra* OR 3 dimension* AND mammogra* OR 3d AND mammar* OR 3-d AND mammar* OR

three dimension* AND mammar* OR 3 dimension* AND mammar* OR 3-d AND breast* OR three dimension* AND breast* OR 3 dimension* AND breast* OR 3D AND breast*

Records retrieved: 456
Date of Registration after 07/11/2016: 34

PubMed

Se-arch	Query	Items found
#18	(#16 and #17)	311
#17	pubmednotmedline[sb]	1831939
#16	(#14 not #15)	6214
#15	(Animals[mh] not Humans[mh])	4298409
#14	(#1 or #2 or #3 or #4 or #13)	6679
#13	(#11 and #12)	1026
#12	(#7 or #8 or #9 or #10)	451588
#11	(#5 or #6)	10908
#10	Mammography[mh]	26465
#9	(Breast[mh] and Neoplasms[mh])	23309
#8	"Breast Neoplasms"[mh]	246831
#7	((breast*[tiab] or mammar*[tiab] or mammogra*[tiab]))	419527
#6	((Hologic*[tiab] or Siemens*[tiab] or "GE Medical"[tiab] or Fuji-film*[tiab] or Phillips*[tiab] or Giotto*[tiab] or PlanMed*[tiab]))	8396
#5	((tomosynth*[tiab] or "tomo-synthesis"[tiab] or DBT[tiab]))	2567
#4	(Mammography[mh] and "Imaging, Three-Dimensional"[mh])	396
#3	(((3d[tiab] or "3-d"[tiab] or "three dimensional"[tiab] or "3 di-mensional"[tiab]) and (breast* [tiab] or mammar*[tiab])))	5493
#2	(((3d[tiab] or "3-d"[tiab] or "three dimensional"[tiab] or "3 di-mensional"[tiab]) and mammogra*[tiab]))	635
#1	(("Selenia Dimensions"[tiab] or Mammomat*[tiab] or Nova-tion*[tiab] or "Inspiration 3D"[tiab] or "Inspiration Prime"[tiab] or SenoClaire*[tiab] or "Seno Claire"[tiab] or Senograph*[tiab] or "Aspire Innovality"[tiab] or "Aspire F"[tiab] or "Aspire S"[tiab] or Cristalle*[tiab] or Diagnost[tiab] or "Phillips Micro-dose"[tiab] or Giotto*[tiab] or "Clarity 3d"[tiab] or "Clarity 2d"[tiab] or "Nuance Excel"[tiab]))	313

Norwegian Institute of Public Health
September 2017
P.O. Box 4404 Nydalen
NO-0403 Oslo
Phone: +47 21 07 70 00

Norwegian Institute of Public Health