Digital breast tomosyntheis – the future screening tool for breast cancer?

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Principal Investigator: **Solveig Hofvind**, Professor, Head of the Norwegian Breast Cancer Screening Program, Cancer Registry of Norway, Oslo and Akershus University College of Applied Sciences, Oslo, Norway.
Project group: **Hildegunn S Aase**, Chief radiologist at the Breast Center at Haukeland University Hospital Bergen, Norway; **Lars A Akslen,** professor, pathologist, Gade, Haukeland University Hospital, Bergen, Norway; **Turid Aas,** surgeon, Haukeland University Hospital, Bergen, Norway; **Sophia Zackrisson**, associated professor, radiologist, Departments of Radiology, Bioengineering, and Materials Science & Engineering, Stanford University School of Medicine, Stanford, California; and Diagnostic Radiology, Department of Clinical Sciences in Malmö, Lund University, Lund, Sweden; **Nehmat Houssami,** professor, MD, University of Sidney, Austalia; **Per Skaane**, professor, radiologist, Oslo University Hospital Ullevaal, Oslo, Norway**; Kristin Pedersen,** MSc, physicist, The Norwegian Radiation Protection Authority; Osteras, Norway; **Sofie Sebuødegård,** BSc, Statistician, Cancer Registry of Norway, Oslo, Norway; **Steinar Tretli,** professor, Statistician, Cancer Registry of Norway, Oslo, Norway, **Tron A Moger,** associated professor, Statistician, Department of Health Management and Health Economics, Institute of Health and Society, University of Oslo, Norway.

1. Relevance relative to the call for proposals

Breast cancer is the most common cancer in women worldwide (1), also in Norway where about 3000 women are diagnosed annually (2). About 1/3 of the cases are diagnosed among women screened in the Norwegian Breast Cancer Screening Program. Screened women are shown to have 40% lower breast cancer mortality compared to non-screened women (3-5). Women with screen-detected cancer are diagnosed in an earlier stage and more often treated with breast conserving treatment instead of mastectomy compared to non-screened (6). However, mammographic screening is also associated with negative aspects like increased incidence of slow growing tumors that would not have been diagnosed during the women's lifetime if she had not attended screening (overdiagnosis), overtreatment and false positive screening results. Mammographic screening is thus capable to improve by increasing the sensitivity and specificity of the screening test.

Three-dimensional digital breast tomosynthesis (DBT) is a new screening tool, which is argued to be better than standard digital mammography (DM) (7-17). The statement is based on a lower recall rate (call-back for further examination after abnormal findings on the screening mammograms) and a higher rate of screen-detected cancer. The basis for the statement is three prospective studies (7-9) and eight retrospective (10-17). However, all the retrospective studies are performed in the U.S. where the screening differ substantially from how it is performed in Norway and Europe (18, 19). In addition, the statement is based on results from two vendors only, Hologic and Siemens.

2. Aspects related to the research project

Background and status of knowledge: DM is the most commonly used screening tool to detect breast cancer in Europe today (20). DM was fully implemented in the Norwegian screening program in 2011. However, the sensitivity of DM is as low as 50% for women with mammographic dense breasts (21) and studies have shown 4-5 times higher risk of breast cancer in women with dense versus fatty breast (22). Whether women with dense breast should be screened with other technologies as DM is thus discussed.

DBT has potential to reduce the effect of tissue superimposition and capable to improve the sensitivity of the interpretation for some examinations. The technology is often used adjacent to DM. Some vendors offer synthetic two-dimensional DM generated from the DBT data (2D) and studies have shown similar detection rate as of additional standard DM (23-25). A systematic review from 2013 concluded that two-view DBT had equal or better accuracy compared with two-view DM, while one-

view DBT did not have better accuracy than two-view DM (26). The review highlighted the urgent need for large screening studies of this technology to complement the available evidence.

Studies on performance measures: *Prospective studies:* The STORM-trial in Italy (8), the Oslo trial in Norway (7), and the Malmo-trial from Sweden (9) compared performance measures (i.e. recall rate, cancer detection, positive predictive value, tumor characteristics) within women screened with DM and DBT with DM or 2D. The STORM trial compared the outcome of sequential screen-readings; the same radiologists read DM first, and thereafter DBT. A significant higher rate of screen-detected cancer, 2.7/1000 and a lower recall rate was found for DM+DBT compared with DM. The Oslo trial assigned the radiologists to read DM or DM+DBT. They found an increase of 1.9 cancers/1000 screens using DM or 2D+DBT. The additional cancers were mostly invasive cancers. The recall rate decreased. The Malmo-trial compared the outcome of two-view DM with one view DBT. A significant increase of 2.6 cancers/1000 screened for one-view DBT was observed. The recall rate increased. The majority (17 of 21) of the cancers were invasive. *Retrospective studies:* Results from eight retrospective studies of DBT adjunct to DM are available of today (10-17). All the studies are conducted in the U.S. where the screening protocol differ substantially from the one used in Norway and Europe (18). Two of the studies (12, 13) compared performance measures before and after the introduction of DBT, while Haas et al. (10) compared the outcome of DM versus DM+DBT within the same timeframe. A clear trend toward a higher rate of screen-detected cancer and a reduction in recall rate were observed in all the studies.

Economic studies: Only two studies, both from the U.S. have considered the costs of DBT (27, 28). One of the studies concluded that DM+DBT resulted in cost savings compared with standard DM in a simulated screening cohort, mainly due to fewer recalls and earlier diagnosis, while the other study found that DM+DBT might be cost-effective for women with dense breasts.

Gaps of knowledge related to DBT: Using DM+DBT seems to have the potential to decrease the recall rate, and to increase the positive predictive values of recalls (PPV-1) and needle biopsies (PPV-2), and the rate of screen-detected cancer, while the issue of interval cancer and cancer rate in the subsequent screening round is unknown. However, the results available of today is performed on equipment's from two vendors only, Hologic and Siemens. Equipment from the different vendors differ in constructions and the outcome is possibly different according to image quality, doses and outcome measures. No studies have reported results from screening women with DBT from GE, as far as we know. We expect 2D+DBT to have limited influence on recall rates in Norway since the rate is already as low as 2-3%, which is substantially lower than in the U.S. (18). Conversely, PPV-1 and 2 have potential for improvements. PPV-2 is not reported in studies using DM+DBT, so far. The effectiveness of mammographic screening is usually measured in terms of reduction in breast cancer mortality, rate of over-diagnosis, and interval cancer. To estimate these measures, 10 and 2-4 years of follow-up, respectively is needed (29, 30). It is not respectable to wait that long to state an effect, given the available data showing a higher detection rate by using DBT. The benefit of the increased detection rate is however controversial due to the issue of over-diagnosis. It is thus of substantial importance to figure out prognostic and predictive histopathological characteristics of the tumors detected with DBT versus DM.

An issue related to DBT is the increased radiation dose if DM is performed adjacent (26, 31). Using one view DBT may result in reduced dose compared with two view DM (32), while 2D+3D minimise the additional dose (32). Doses are shown to vary between vendors (33).

The economic aspects of implementing DBT is only reported from models based on data from the U.S. (27, 28). The results can hardly be transferred to Norway. Our project has the potential to explore all the parameters mentioned above.

Approaches, hypotheses and choice of methods: The Norwegian Breast Cancer Screening Program started as a pilot in four counties in 1996 and became nationwide in 2005 (18). Hordaland was one of the pilot counties. Further assessment take place at one of the 16 breast clinics in Norway. Haukeland University Hospital is the breast centre for Hordaland.

We want to take advantage of the new mammographic equipment (Seno Claire GE Breast Tomosynthesis) installed at the screening unit at Danmarksplass in Bergen, December 2014, and perform a randomized trial assessing 2D + DBT in two projections (hereafter referred as tomo) versus standard two projections DM as screening tools. The equipment is accepted for screening both in the US and Europe, but no results from studies on human beings are reported in articles of today (34, 35). Measuring the effect of tomo with GE versus standard DM can be done by comparing results of early performance measures and economic aspects in two comparable populations at the same age and residing in the same county, examined by the same radiographers, screen-read by the same radiologists and histologically breast cancer proven by the same pathologists, treated by the same surgeons and oncologists.

The project has a practical and an academic part: 1) The practical part is critical and consists of a four months pilot and 24 months (one screening round) of running the trial. The pilot is aimed at testing feasibility including the time aspect, get experiences and learn how to read tomo, develop a practical hanging protocol and a form to report information needed to assess the research questions right after the screening is performed and eventual diagnosis is stated. The trial will be run as a part of the screening program. Only small changes from the usual setting is acceptable. 2) The academic part aims at investigating early performance measures and economic aspects performed in the practical part. We aim to address the following topics and research questions in the academic part:

Study I: *Early performance measures in a population based screening program using tomo versus DM –interim analyses.* We will compare results of early performance measures.
How do the recall rates, including false positive screening results differ between the two groups? What time is spent in examination and reading with the two technologies? How do the radiation doses differ between the two groups? Due to the small number of women screened and diagnosed with breast cancer during the first year (Table 1), this study will focus on early performance measures related to the time used, recalls and radiation dose. We will compare the outcome for tomo versus DM and according to recommended levels given in the quality assurance manual (36) using standard statistical tests (37).

Study II: *Use of tomo versus DM in a population based screening program – a randomized controlled trial.* This study deal with the epidemiologic and radiologic aspects of the project.
How do the recall rates, including false positive screening results differ between the groups? How do the rates of screen-detected DCIS and invasive breast cancer differ? How do the PPV-1 and PPV-2 differ between the two groups? How do the mammographic features in screen-detected cancers differ between the two groups? The results will include results from the entire study period. The number of women and cases will be approximately twice as much as Study I. The same statistical approach as in Study I will be used.

Study III: *Prognostic and predictive histopatologic characteristics of breast tumors detected in a population based screening program using tomo versus DM.* This study focuses on prognostic and predictive histopatologic characteristics of the tumors.
How do the prognostic characteristics (morphology, tumor size, histologic grade and lymph node involvement) differ between the two groups? What about stage distribution? How do the predictive characteristics (estrogen (ER) and progesterone (PR) receptor status, Her2Neu and Ki67) differ?
What about subtypes based on immunohistochemical analyses and Nottingham Prognostic Index?

Low stage Luminal A-like tumors might indicate low progression compared with late stage Her2+ or TN tumors. Differences in distributions of the characteristics, and thus different treatment algorithm between the tomo and DM groups might indicate whether the tumors detected with tomo represent low progression compared with those detected with standard DM. Descriptive analyses will compare rates and percentages. Logistic regression analyses will be used to estimate the odds of having breast cancer with specific characteristics diagnosed (37).

Study IV: *Tomo and DM in a population based screening program – which technology has the highest sensitivity for women with mammographic dense breast?* We will stratify analyses on early performance measure of tomo versus DM by density, using Volpara® density measure.
How do the early performance measures given in study II+III differ by mammographic density?
Volpara® is installed at the screening units at Danmarksplass and data is available for this study. We will use descriptive analyses to compare distributions and rates, while logistic regression analyses will be performed to estimate the odds ratio of recalls and breast cancer (37).

Studies V and VI: *Costs of tomo and DM in a population based screening program – Is tomo cost-effective?* Study V will deal with early costs related to time spent at screening and reading, the recall rates, diagnostic procedures, treatment and total costs for the two techniques. Data from the first year of the trial will be used. A previous study from Norway, which showed that treatment costs are highest during the first year following a diagnosis will serve as a methodological basis for the analysis (38). Using a similar approach, we will compare treatment costs for interval cancers, recurrence and early costs of cancers detected in the following screening round, using the full two year follow-up in Study VI. Results will be presented as cost per recurrence, interval and subsequent breast cancer avoided. Possible differences between groups in these outcomes should be well captured during the two years. Mortality may also be used as an additional outcome in the cost-effectiveness analysis in If the project is sufficient funded, study VI, although the follow-up time is too short, will use a simulation model with mortality estimates from the Cancer Registry. Additional cost estimates for the period beyond two years will be run (33) as inputs can be run to estimate the cost-effectiveness in the life-long perspective for the women (as e.g. in (28)). A major advantage of Studies V and VI compared with the U.S. studies (24, 25), is the availability of individual level data within the project, thus avoiding most assumptions of recall rates, cancer stage distributions, diagnostic and treatment costs etc. from earlier studies. This ensures a higher level of detail when defining the list of cost components, and more precise estimates of the variation across patients in both effect outcomes and costs.

A prospective cohort study: We will perform a prospective cohort study. During the study period, about 45,000 women will be invited to screening at Danmarksplass and 35,000 (75%) are expected to participate (Table 1).

Table 1: Number of women in the target group of the Norwegian Breast Cancer Screening Program, Hordaland - Danmarksplass, estimated number of participants, recalled women and breast cancer cases in the planned project

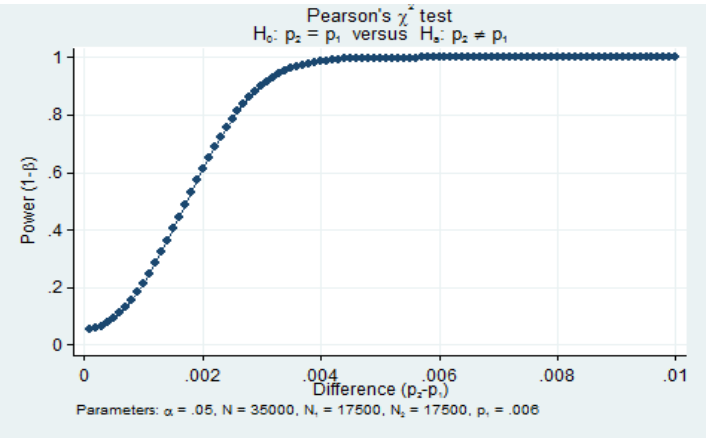
	Total	Control group DM	Study group Tomo (Synthetic DM+DBT)
Target group (n)	45 000	22 500	22 500
Extpected participants *	37 500	17 500	17 500
Expected recalls*	3%	525	525
Expected screen-detected cancers*∞	6.0/1000	105	105
Intervalcancer*	2.0/1000	35	35

*Based on numbers from 2013 and 2014; ∞Screen-detected ductal carcinoma in situ (DCIS) and invasive breast cancer

Randomization: The women targeted our study will be invited to the Norwegian Breast Cancer Screening Program, at Danmarksplass, as usual. The women are residing in rural and urban areas in Hordaland county. All attending women will be asked if they are willing to participate in the study after they have received written and oral information about the study from the radiographers. Those who accept the invitation will sign an informed consent that the radiographers will be responsible to collect, before they are randomized into tomo (intervention group) or DM (control group). Experiences from the Oslo Tomosynthesis Trial shows that about 98% of the women who were asked, agreed to take part in the study. About 70% of the attending women were asked. Those who do not agree to participate in the planned study will be screened with DM. Their data will not be included in our study.

Power estimations: Using the populations given in Table 1 indicate that the difference between DM and tomo have to be 0.25% or more to be statistically significant different in the two groups, given a power of 0.8 and a p-value of 0.05 (Figure 1).

Figure 1: Estimated power for a two-sample proportion test for the expected number of women included in the study



Screen-reading: Seven breast radiologists will be involved in the reading. Results from the Oslo Tomosynthesis Trial showed that reading tomo required 30 seconds more/each exam compared with DM. A reading schedule will ensure that all radiologists read the same number of tomo and DM. All screening exams, regardless of technology used, will have the same independent double reading as the usual procedures in the screening program.

3. The project plan, project management, organisation and cooperation

This project is aimed at performing a randomized trial investigating the effect of early performance measures and economic aspects of tomo versus DM in a screened population. All studies will be performed with data from women screened at Danmarksplass. The pilot will be performed Aug-Dec 2015, while the trial period is set to Jan 2016-Dec 2017 (Table 2). Complete data for analyses of early performance measures related to the screening exam will be available after the end of the trial. However, we will follow the women for information about treatment and therapy, interval and breast cancer in the next screening round, recurrence and metastasis, two years after screening exam. These follow-up results are of utmost interest for the complete effect of tomo versus DM in a clinical and economic perspective.

Data collection: All studies will be based on the same dataset, except for # I and V, which are based on data collected from the first year of the trial.

Clinical data: Data related to screening participation will be extracted from the Norwegian Breast Cancer Screening Program's Database, located at the Cancer Registry of Norway. Technical data regarding mammographic density and radiation doses is considered part of the screening data. Data related to needle biopsies and treatment will be collected immediately after the diagnosis, particularly for this study, for the study period (2016-17) and the follow-up time (2018-19). These data is needed immediately to keep the study results updated and to keep the time schedule. A close collaboration with the pathologists and surgeons at Haukeland University Hospital (Professor Akslen and Dr Aas)

is already established. Research assistants will be responsible for collecting, reporting, and coding the trial and follow-up data.

Data for cost analysis: Information on investment cost for tomo will be gathered from the breast center. Estimates on the costs of tomo versus DM will be based on the recorded time used for each method for each patient. All interventions, whether diagnostic or treatment, performed on the patients during follow-up are routinely collected with relevant procedure codes within the project. Costs for each procedure are estimated using either radiology reimbursement weights (diagnostic procedures), DRG cost weights (for in-hospital treatment such as surgery, radiotherapy and chemotherapy) or retail sales prices (hormonal therapy). The approach evades waiting for data on resource use from the Cancer Registry, the Patient Registry and the Prescription Registry, which all have a lag in their data update of at least half a year.

Organizing the work: Professor Hofvind will be responsible for the trial. She has substantial knowledge about the screening program, the database and she has extensive experiences in leading studies, also regarding tomosynthesis, by her involvements in the Oslo Tomosynthesis trial. She will be the main supervisor for the applied PhD student. The medical leader of the breast centre at Haukeland, Dr. Aase, will be responsible for the radiologic part of the trial, while professor Akslen will take care of the histopathologic part and Dr Aas the surgical/oncologic part. Associate professor Moger will lead the cost analysis. Moger was highly involved in the economic part of the research-based evaluation of the Norwegian Breast Cancer Screening Program. Sebuødegård is a statistician with particular knowledge in data management and the screening database. She will play an important role in data extraction and data cleaning. She will support the applied PhD student in the statistical part, with professor Tretli as a mentor. Professor Skaane, who has led the Oslo DBT trial, will co-supervise the PhD-student in collaboration with associate professor Zackrisson and professor Nehmat. Zackrisson has substantial experience from mammographic screening, and she is running a DBT trial in Malmo. Professor Houssami co-led the STORM trial and was responsible for writing the chapter about screening modalities in the IARC Handbook of breast cancer screening (5).

Table 2: Time schedule and milestones for the planned project

Feb-Sept 2015	Apply the Regional Ethical Committee, plan the pilot
Sept-Dec 2015	Piloting – detailed planning of the main project
Sept 2015-Des 2018	Hiring research assistants – responsible for the practical part of the study, collecting, reporting and coding the histopathologic data
Jan 2016-Dec 2017	Running the trial
Jan 2017-Dec 2019	Hiring a PhD student
Jan-Dec 2017	Application for PhD + reviewing the literature Analysis and writing paper I – submission to a peer-reviewed journal
July-December 2017	Preparing programming code for cost data and analysis based on preliminary data
Jan 2018-Sept 2018	Analysis and writing paper II+V – submission to a peer-reviewed journal
Aug 2018-Dec 2018	Analysis and writing paper III – submission to a peer-reviewed journal
Oct 2018-Mar 2019	Analysis and writing paper IV – submission to a peer-reviewed journal
Oct 2018-Mar 2019	Evt Cost analysis – finalizing and submitting papers VI
Feb 2019-May 2019	PhD student: Working with the thesis – finalizing
May 2019-Dec 2019	Finalizing the papers, the project, and prepare for disputation
Dec 2019	Disputation
Jan 2020-Dec 2020	Finalizing the study: Analysing rates, histopathologic characteristics and mammographic features of interval and subsequent breast cancer – on own budget

Budget: The total cost for the project is 15566K NOK including own costs of 3200K NOK. To adapt the project to the comments from the Norwegian research foundation, we apply for money to do the pilot, performing the randomized trial and to analyse the collected data during the study period. We would like to apply for two full time research assistants (one at the Cancer Registry and one at Haukeland University hospital) who could have served as the glove in this project and played the major role in the practical part of the study and follow-up period, which is basis for success in the academic part. However, the budget is limited and two 75% position during the study period only will help us on track. The research assistants will be responsible for all paperwork, collection, reporting, and coding of the data. This salary will also cover the administrative work related to the trial, at the screening unit. The assistants will be employed from the start-up and during the trial (2015: 2x75% positions; 2016: 2x75% 2017: 2x75%) total costs 2463K NOK. Running a screening trial with tomo requires substantial storage space for the data. We apply for money to support the breast clinic with the expenses related to the storage (in total 400K NOK). The real cost will be about the double. We have estimated 45 additional seconds for reading each screening exam with tomo, 1:30 min for the two readers (n=17,500 exams). We have estimated the extra work related to forms for the cases discussed at consensus and recalled to ensure immediate coding and updates of the results, to be 3 minutes, accounting for a total of 438 hour/year, which represent about 25% of a full time position (623K NOK in total). Due to the importance of understanding the tumor-biology, over-diagnosis and overtreatment, and our focus on the economic aspects of using tomo versus DM in the screening, the pathologists and surgeons/oncologists have to report additional information about the diagnosis and follow-up, particularly for this project. However, the budget do not get any room for the work performed by the pathologists and surgeons, which is critical. We apply for a PhD student for analysing data related to the clinical part of the study (3211K NOK) and a 25% position in 2017-19 for a researcher to do the economic analyses related to the trial (803K NOK). Statistical support and supervision are not included in the budget, neither is data extraction from the databases at the Cancer Registry, nor analyses of the follow-up, interval breast cancer and breast cancer diagnosed in the screening round following the screening round with tomo. That work and the work by the PI will be performed on own costs. The total costs for the study, when adapted to the recommendation given by the research foundation is estimated to be 9843K NOK, whereas 7500K NOK is applied from the Norwegian Research Foundation. We consider the additional costs to perform an excellent study small compared to the outcome of the restricted budget.

4. Key perspectives and compliance with strategic documents

Mammography is the preferable technology for breast cancer screening and diagnostic today. DBT is assumed to be the next generation screening technology for breast cancer (39). As of today, there is not sufficient evidence about the effect of tomo to implement the technology. This study has a unique possibility to contribute in filling the gap of knowledge needed to assess the technology's potential as a screening tool. If tomo turn out to be a better screening tool compared with DM, the benefits of participating in screening might be improved, whilst the harms will assumingly decline, which is beneficial both for the women screened negative and those diagnosed with breast cancer, both in Norway and in other countries.

Interim analyses will be performed after one year of performance of the study, while the final results will be available 3-6 months after the trial is finished. This is unique in a screening setting. In addition, we will follow the women for interval and subsequent cancer 2 years after the trial is finished. Results from the applied trial and the follow-up represent a unique possibility to analyse data from a substantial number of screened women which no other screening programs are able to do, due to the link between the clinical data, the screening database and data from the incidence database at the Cancer Registry. Norway is in a unique situation with the 11-digit PIN number, the

nationwide screening program and the Cancer Registry, which makes it possible to identify the cancer cases, even if women move from one county to another. These facts make this study unique from an international perspective.

The trial might be able to serve as an example for other screening and diagnostic tests, not only breast cancer and mammographic screening. Implementing new technology should be based on sufficient evidence. This protocol has the possibility to serve as a guide for testing screening and diagnostic tools for other diseases.

Radiographers, radiologists, pathologists, surgeons, and others working at the breast clinic and with breast cancer at Haukeland University Hospital will be engaged in the project. The breast centre will thus gain a lot of positive attention, both from the population and stakeholders. The project and the knowledge gained by running the trial will be of great interest not only in Norway, but also internationally. The project group includes highly experienced people in radiology, particularly tomo, epidemiology and statistics, which indicate high validity and makes it possible to run the project effectively.

Relevance and benefit to society: All Norwegian women aged 50-69 years are invited to participate in the screening program. The effectiveness of the program is measured by its effect on society (among invited women) and per protocol (participants). A higher sensitivity of the test will thus lead to increased effectiveness in both perspectives.

Environmental impact: It is well known that replacing screen film mammography with digital mammography have pulled away the use of developer in the imaging. This was a substantial step toward an environmental cleaner screening tool. Tomo will have the same environmental-friendly approach regarding the imaging.

Ethical considerations: The data collection will be performed according the Cancer Registry regulations and Helseregisterloven § 8, 7th edition (38). Only information from women who have signed an informed consent will be used. The PhD student will receive de-identified data. The linkage key between the PIN and ID will be stored at the Data Delivery Unit at the Cancer Registry. The project is applied the Regional Ethical Committee (Reference 569184).

Gender issues: Mammographic screening is only women only. No men are thus included in the project.

5. Dissemination and communication of results

All studies will be submitted to peer-review international journals, preferably in the field of radiology, breast oncology, epidemiology, and health economy. Potential journals for paper I and II are "Eur J Radiology" and "Radiology", respectively. Study III is focusing on histopathologic issues, whereas "The Breast" is a potential journal for publication. Paper IV includes mammographic density and is thus entering the field of stratified screening by risk factors, which is a hot issue in the screening field. We will submit that paper to "Cancer". The fifth paper, dealing with economic aspect related to tomo as a screening tool will be considered for submission in Journal of Health Economics. The Research Council of Norway will be gratitude in the acknowledgement in all publications. The research group will encourage the PhD student to submit abstracts to national and international congresses in order to build network within the field mammography, radiology, and tomosynthesis. We will also make summaries of the project and results of the studies available for the women in the target group of the screening program, the public, the professionals involved, health politicians, and stakeholders. We will use Mammonett, an internal webpage for professionals working in the Norwegian Breast Cancer Screening Program, and the homepage of the Cancer Registry of Norway, to inform both women targeted by the screening program and the general population about the project. The results of the study will also be presented at the annual

meeting for the staff working in the screening program. A press release will be submitted when the papers are available online or in printed version.

The communication between the clinical and analytic part will be taken care of by the research assistant and the PI. The PhD student and the researcher will regularly present results to the staff at the breast clinic at Haukeland University Hospital, to keep the staff informed and motivated.

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