Adapting Breast Cancer Screening Strategy Using Personalised Risk Estimation

## Reporting

### Project Information

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**Executive Summary:**

ASSURE - Adapting Breast Cancer Screening Strategy Using Personalized Risk Estimation - consisted of 10 project partners from 7 countries with leading expertise in the field of breast imaging, with the Radboud University Medical Center Nijmegen as the coordinating partner. The project started in December 2012 and has ended November 2015 and was supported by the European Commission under the 7th Framework Programme for Health Research.

While early detection of breast cancer by screening appears effective at the population level, many women do not benefit from screening: 30% of breast cancers in women who are screened on a regular basis are not detected by screening or are detected at a late stage. As a consequence, still many women...
participating in screening die from breast cancer. It is recognized that a big limitation of screening is the way it is currently organized: As a one-size-fit all approach with one technique, irrespective of personalized risk factors and not looking at suitability of the mammographic screening test for the individual. There are opportunities to improve this situation, since it is known that some women are at a much higher risk of getting the disease than others, and that mammography is unsuitable for early cancer detection in women with dense breasts.

In the project new personalized screening protocols were developed based on image analysis and machine learning techniques that quantify risk patterns based on the distribution and amount of mammographic density. To study effectiveness of the methods large databases of screening mammograms were collected from screening programs in the UK, Denmark, and the Netherlands. Mammograms of over 50,000 women comprising over 100,000 screening exams were used in the final analysis. Significant relations were found between new imaging biomarkers developed in the project and breast cancer risk. The reduced performance of mammography in women with high density was accurately modeled.

ASSURE partners also contributed to the development of techniques making screening with alternative imaging modalities more feasible. Advanced software applications for automated breast ultrasound and breast MRO were developed and validated that may expedite introduction of more sensitive screening methods for women who need them.

Personalized risk estimation and breast density measurement allows stratification of population-based screening programs based on both risk of cancer and risk of masking. Two risk models to provide personalized estimates were developed. The first uses risk factors derived from the routine mammogram only, while the second includes other known risk factors in addition to mammographic variables. The cost-effectiveness of using stratification based on personalized risk estimation was estimated in a cost-effectiveness analysis. Stratified screening is likely to be cost-effective compared to current programs in European populations although the optimal stratification protocol is uncertain.

Project Context and Objectives:
Breast cancer is the most common cancer that affects women, with 421,000 new cases diagnosed in the EU each year and 129,000 women dying from the disease [Ferlay Eur J Cancer. 2010]. While causes remain largely unknown, incidence is still increasing in most countries. Currently, approximately 1 in 8 women develop breast cancer during their lifetime. If breast cancer is detected early, mortality is decreased due to more effective treatment options. Furthermore, the quality of life of these women is maintained because early detection enables less radical treatment. Screening programs have therefore been introduced to detect early breast cancers in asymptomatic women.

The positive effect of breast cancer screening on mortality has been demonstrated in reviews of large population based programs. Breast cancer mortality reductions between 24% and 48% have been reported among women who regularly attend screening. However, despite these clear benefits, still a substantial number of women, even though they perfectly comply with screening protocols, die from breast cancer. Approximately 30% of breast cancers are detected in-between screenings (interval cancers) and 25-30% of screen-detected cancers is retrospectively detectable on previous mammograms, and thus could have been detected earlier. This constitutes a clear need for improved breast cancer screening. The avoidable mortality that results from the suboptimal performance of current breast cancer screening was the key societal driver of the ASSURE project.

The major shortcoming of current day breast cancer screening is the one-size-fits-all approach that is
currently applied for the majority of women in a specific age range; they all undergo the same screening protocol, with the same diagnostic modality (X-ray mammography, MG) and at the same fixed interval. The only exception is the recommendation to use MRI screening in women with a lifetime risk to develop breast cancer of more than 20-25% (US and EU guidelines). This encompasses roughly 1% of women who mostly carry the rare BRCA gene mutations.

It is known that some women are at much higher risk to develop breast cancer or have breasts that cannot be imaged well with X-ray mammography. After age and the rare BRCA mutations, breast density (or mammographic density) is the strongest breast cancer risk factor known to date: women with dense breasts (> 50% glandular tissue), comprising approximately 35-40% of women of screening age, have shown to have a three- to six-fold increased risk of developing breast cancer compared to those with little or no dense tissue. On top of that, the sensitivity of mammographic screening is seriously impaired in women with dense breasts. This reduced sensitivity is due to the fibro glandular and stromal tissues (dense tissues) having the same X-ray attenuation properties as tumors and thus both showing equally bright on mammographic images (Figure 1).

This causes tumors to be masked for radiologists and thus breast cancer to remain undetected. As approximately 35-40% of the screening population has dense breasts, the huge impact of this limitation of current day breast cancer screening is evident. For a group as large as 40% of all women in the screening programs, current mammographic screening falls short. This group of women has the highest risk of developing breast cancer, but their dense breast tissue severely limits the effectiveness of X-ray mammography.

Women are becoming more and more aware of these problems with breast cancer screening and demand insight in their breast density. These claims have already been ratified by several courts in and outside Europe. The concerns increasingly voiced by women caused by this awareness together with the unavailability of adequate alternatives were the political driver of this project: The individual woman needs to be assured of the best possible screening solution.

The objective of the ASSURE project was to investigate and develop new technologies that can enable introduction of personalized screening protocols, that optimally makes use of alternative screening modalities to account for the difficulties involved with screening dense breasts. To account for breast density of a specific woman in her screening regimen, several scientific obstacles need to be overcome:

- The current standard for breast density assessment, visual estimation by radiologists, is not acceptable for stratification in screening practice. Informative quantitative measures need to be developed and validated that capture the full complexity of breast density in relation to risk and mammographic sensitivity in a reproducible way.
- The current use of imaging modalities that better suit women with dense breasts, such as MRI and ultrasound, have limitations. The clinical work flow for these modalities has to be adapted to be able to handle the increased amount of women that need to be imaged and diagnosed with these modalities.
- Current risk models for the general (screening) population have not been very successful at determining a woman’s individual risk. Incorporation of new quantitative, volumetric and breast density pattern measures, based on digital mammography, could lead to greater accuracy.
- There is no cost-effectiveness framework that enables the optimisation and validation of a multi-modal and personalised screening protocol. Furthermore, this model should be applicable to the diverse screening programs and the associated health care systems in the different EU Member States and
Partners in the ASSURE consortium performed the necessary investigations to expedite the introduction of personalised stratification and improved screening protocols that account for risks associated with breast density and breast density patterns, together with the other major risk factors. ASSURE was driven by four European SMEs. They took the lead in the development of the required tools for personalised breast cancer screening, supported by development of the scientific basis by the research partners and validation opportunities offered by the clinical partners.

To assess breast density, radiologists currently visually estimate the relative amount of dense tissue. These subjective estimations suffer from high inter and intra-observer variability. This lack of standardisation seriously compromises the current predictive value of risk assessment based on breast density and their integration in screening protocols. To address this issue, methods were being investigated to objectively quantify breast density in mammograms. Additionally it was expected that completely new methods based on the analysis of breast density patterns and changes of these patterns over time can further boost the performance of breast density as a risk factor. Within this project, these innovative markers were investigated and related to both the risk of developing breast cancer and the risk of missing a cancer on X-ray mammography. This enables the stratification of patients that cannot be screened optimally by standard X-ray mammography.

Screening modalities such as MRI and ultrasound could act as a supplement or alternative for screening of women with dense breasts. However, they are in their current state not applicable in high volume screening. In the project new techniques were developed to make screening with these new modalities more cost-effective. Together, X-ray mammography, MRI and Automated Breast Ultrasound (ABUS) can address the entire screening population. In the ASSURE protocols, for the general population X-ray mammography, MG, will be used. Women with increased risk can be screened with a combination of MG and ABUS, and women with the highest risk profile can be imaged with a combination of MG and MRI.

Most of today's breast cancer risk models ignore breast density as a personal risk factor, or fail to successfully implement this feature. This is partly due to the complex nature of the relation between breast density and personal breast cancer risk and the lack of objective quantitative measures to characterise breast density. Inclusion of the objective methods as will be investigated in this project are expected to substantially contribute to the ability of risk models to predict individual risks.

In summary, ASSURE aimed at development of a cost-effective and ready to implement personalised breast cancer stratification and screening protocol together with the necessary tools and methods. Adoption of this protocol will minimise the risk of a particular patient to have a cancer missed at an early stage, resulting in decreased mortality and increased quality of life due to less radical treatment options, and thus substantial benefits for women participating in screening programs.

Project Results:
Breast density and risk
In the project Volpara was used to measure breast density. Volpara is a software package developed by Matakina, one of the partners in ASSURE. It analyses a digital mammogram and produces a value that can be used by radiologists, epidemiologists, and the wider clinical community to help determine volumetric breast density using an automatic, objective and reproducible method. The software reports three readings of interest: the percentage of the breast that is occupied by dense tissue; the absolute volume of dense tissue in cm³; and the total volume of the breast. The Volpara Density Grade (VDG) was

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developed as an addition to software to provide a means of converting the continuous volumetric density value computed by Volpara to a categorical (qualitative) scale as used by radiologists for their visual readings. It correlates scientifically with the BI-RADS density classification which enjoys widespread use and acceptance.

In ASSURE the Volpara software was extensively validated using breast MRI data as a reference. We included in the evaluation studies for which breast MRI data and FFDM were available with time interval between these exams of less than two months. We obtained 250 MRI volumes and 928 corresponding mammographic images from 132 women. Mean time between MRI and mammography acquisitions was six days. The age of the screened women ranged from 24 to 77 years, and was 46.5 ± 11.10 years on average. The MRI images were segmented automatically using dedicated software developed in the project. This allowed accurate computation of both the relative and absolute amount of breast density per breast. An example of a segmented breast MRI exam is shown below.

It was found that volumetric breast density and breast tissue volumes obtained with Volpara were highly correlated with MRI measurements. Results show that Volpara tends to underestimate breast density in very dense breasts. This effect has also been observed in other methods for volumetric breast density estimation. Like Volpara, these methods are also based on a physics-based image model and use a set of pixels of the breast that belong to fatty tissue as an internal reference to predict fibro glandular tissue thickness. The selection of the internal reference is more complex in dense breasts than in fatty breasts, and this affects the calibration of fatty tissue attenuation and leads to breast density underestimation. However, the breast density underestimation in dense cases does not appear to affect the final VDG categorization. Thus, we found that it is feasible to obtain accurate measurements of absolute and relative volumes of dense breast tissue from full field digital mammograms. Availability of such measurements is crucial for the development of objective breast cancer risk models and may be used in the development of personalised screening protocols.

To enable researchers in ASSURE to build analysis tools on top of the Volpara, Matakina extended its software with new functionality that gave access to regional breast density maps. These were used in the project to assess focal change of breast density over time. These breast density maps were also used extensively in the development of new algorithms aimed at quantification of typical density patterns associated with breast cancer risk. Researchers of the Danish company Biomiq and the University of Manchester used machine learning to identify features that represent breast density textures that may separate women into different risk categories.

High mammographic density, assessed using BI-RADS density categories on film screen mammograms, is known to negatively influence breast cancer screening performance. However, to what extent breast density affects screening performance in programs using modern digital mammography systems is not known. Therefore, we determined to what extent volumetric mammographic density, measured automatically, influences screening performance when using digital mammography. For this purpose a large consecutive collection of screening exams was used collected in the Dutch screening program between 2003 and 2011. The study involved 111,907 exams in 53,243 women, and included all cancers identified in these women in the study period: 667 screen-detected cancers and 243 interval cancers. We determined screening performance measures for four density categories comparable to the Breast Imaging-Reporting and Data System (BI-RADS) density categories.

It was found that 21.6%, 41.5%, 28.9% and 8.0% of the examinations were categorised as density
category 1 (‘almost entirely fatty’) to 4 (‘extremely dense’), respectively. In total, 667 screen-detected and 243 interval cancers were identified. Cancer detection rates were 4.0, 6.4, 6.6 and 6.8 per 1000 examinations in categories 1 to 4 respectively (\(p\)-trend<0.001). Interval cancer rates per 100 exams were higher in higher density categories: 0.7, 1.9, 3.0 and 4.5 respectively (\(p\)-trend<0.001). Screening sensitivity, calculated as the proportion of screen-detected among the total of screen-detected and interval tumors, was lower in higher density categories: 85.7%, 77.0%, 68.4%, and 60.4% respectively (\(p\)-trend<0.001). False positive examinations occurred more frequently in women with dense breasts: 1.1%, 1.5%, 1.8%, and 2.4% in categories 1 to 4, respectively (\(p\)-trend<0.001).

Table 1: Screening performance in different density categories.

In conclusion, automatically measured volumetric density on DM, impacts screening detection measures along the same patterns as established with BI-RADS density. Since measuring breast density fully automatically has much higher reproducibility than visual assessment, this automatic method could help with implementing density-based supplemental screening. Results form an important resource for investigations of cost-effectiveness of personalised screening protocols.

In ASSURE, big databases with screening examinations were collected in three countries, England, Denmark, and the Netherlands, representing different populations with different breast cancer risks and different screening programs. Using this data various aspects of breast density as a marker of breast cancer risk could be investigated. In the following paragraphs we give a description of the three databases, their characteristics and the numbers of women included.

Netherlands Data
Screening mammograms were selected from the PREVENTICON screening center located in the city of Utrecht. Mammographic examinations acquired after December 31, 2011 were excluded, because the linkage with the Netherlands Cancer Registry (for occurrence of breast cancer) is complete only for mammograms taken until 2011. The total database comprised 54,285 women. Women with bilateral breast cancers and women with missing Volpara scores on all mammographic views (n=1161) were not used for data analysis. In the remaining group of women (n=53,070), 886 breast cancers were identified through linkage with the Netherlands Cancer Registry: 625 screen-detected cases based on a screening mammogram taken before January 1, 2012; and 261 interval cancers identified after a negative screening mammogram that was taken before January 1, 2012). For the texture measures that were developed during this project, part of the data from the PREVENTICON database was used as training data. The women, whose mammograms were used for texture training, were excluded from the analyses of the final evaluation. This is necessary because otherwise the performance of the texture measures in the PREVENTICON database would be overestimated. Therefore, for the main analyses, our data comprised 513 women with breast cancer (357 screen-detected and 156 interval breast cancers) and 50,871 women without breast cancer.

UK Data
The Manchester database comprises images and associated metadata of approximately 45,000 women from the Predicting Risk of Cancer at Screening (PROCAS) study in Manchester. For the purposes of this analysis we have included data from PROCAS subjects who were due to have had two screening appointments before December 31, 2014. That is, those subjects who were recruited to the PROCAS study between October 2009 and December 31, 2011, since the period between breast screening sessions is normally 3 years in the UK, and for whom full field digital mammograms were available. Image data for the majority of the PROCAS database (n=40,455 women) have already been retrieved and
anonymised. This dataset did not include images from women who were diagnosed with (and treated for) breast or any other type of cancer before inclusion. Tyrer-Cuzick risk score (TC), age, BMI and HRT scores are available for each woman. In order to ensure consistency of the dataset we excluded those with non GE images in their study folder (n=1027), those with breast implants (n=10), mammograms missing one or more of the four views (n=636), records with missing BMI values (n=2876) and/or missing VolparaTM scores (n=1413), data from women either younger than 47 (n=275) or older than 73 (n=12) and finally data from women who did not consent to their data being used for further research (n=269). In this process data from one woman may have been excluded due to more than one reasons; therefore the previous sets are partially overlapping. After this stage, we concluded with a dataset consisting of 484 breast cancers and 34,586 non breast cancer cases. 292 of the cancers are first round screen-detected cancers, 147 of them are second round screen-detected cancers and finally 45 of them are interval cancers. The number of interval cancers is expected to increase strongly as the duration of follow-up increases.

Denmark Data

The Copenhagen (CPH) dataset was collected from the population-based breast cancer screening in the Capital Region of Copenhagen, Denmark. The Capital Region comprises Greater Copenhagen and the island of Bornholm. Women are screened for breast cancer biennially from ages 50-69. In 2008 the screening program transitioned to 4-view digital mammography. Raw (For Processing) images were collected for a single screening round from all but one site in the Capital Region for the period November 1st 2012 to December 31st 2013. Screen-detected (SD) cancers are registered during screening. Information on the occurrence of interval cancers will only be available once the full two-year follow-up period has passed (expected mid 2016). Women were excluded when none of the four views was available or when images could not be analyzed (by Volpara or either of the two texture scores). The resulting dataset comprised 54,560 women. 54,140 of these are non-breast cancer cases and 420 are women diagnosed with a screen-detected breast cancer. For all women, age at screening and the collected mammogram is available for analysis. As mentioned above, information on interval cancer status is not yet available. The cancer status for the 420 screen-detected cancers is kept with the Department of Public health of the University of Copenhagen only and thus all density and texture scoring on the CPH dataset has been done blinded.

Density measures and risk

The ASSURE project data sharing agreement stipulated that mammograms could not be copied from partner site to partner site or to a shared (off-site) High Performance Computing (HPC) facility. This implied that each data owning partner (RUNMC, Biomediq, and Manchester) had to score the data they controlled. For this purpose each of the partners established an on-site HPC facility to score their images with respect to density and two texture algorithms (see details below). Since a typical mammography exam includes 4 images (left+right CC and left+right MLO) in total about 600,000 images had to be processed.

Density scoring was performed with Volpara, which produced three continuous scores per image: i) volumetric breast density, the volume of dense breast tissue relative to the total breast volume (VBD, percentage), ii) the volume of the dense tissue (VDT, cm3), and iii) the total breast volume (TBV, cm3). A fourth score, the volume (cm3) of non-dense (fatty) tissue is easily derived as the difference between TBV
Breast density texture measures, representing the spatial distribution of density in the breast rather than its volume, were computed with machine learning methods developed in the project. These methods were trained to identify patterns related to risk on an independent database. Two methods were employed, one developed by Biomediq and one by the University of Manchester. The texture algorithms were trained using only images from the contra-lateral side of diagnosed cancers. For screen detected cancers, this meant using the contra-lateral views from the screening visit where the cancer was diagnosed. For interval cancers, we used contra-lateral views from the screening visit immediately prior to the interval cancer diagnosis. The general training setup for the machine learning based texture score was using an independent case/control dataset: given that both cases and controls were represented by cancer-free mammograms, performance was optimised such that posteriors (risk scores) best segregated (future) cancers from the healthy (undiagnosed) controls. All training and subsequent scoring was done using the density maps generated by Volpara during density scoring. The texture measure from Biomediq was based on deep learning. Results of the combined density measures are shown below. Odds ratios (OR) are given with reference to VDG 2 and the low risk texture score.

The study was designed to both investigate and enhance the joint association between density + texture and cancer outcome. Results demonstrate the “unfolding” of the density axis from a one dimensional view of “amount of dense tissue” to a two-dimension amount and composition view. We observe that the odds ratio for the VDG 2 category with high risk texture T3 was the overall highest for Biomediq texture and the second highest for Manchester texture. This highlights that the combination of density and texture find women at high cancer risk that, using density alone, would be characterised as low risk – the primary goal of using both risk measure simultaneously. We further notice that within each density category, the unfolding by texture generally orders women from low to high risk. Finally, we observe that for Manchester texture T1 in combination with VDG3 the OR does not seem to be higher than both non-reference categories in the VDG 2 column. This could imply that women in this category have an overall lower risk than women with a density grade VDG 2 and perhaps should be treated as lower risk than a density only risk stratification would suggest. For the PROCAS and Copenhagen datasets, the descriptive statistics were consistent with the PREVENTICON results, but odds ratios were lower due to the missing information about the interval cancers.

In summary, density measures have been investigated in three large screening populations for two variants of texture based risk. Both texture scores positively segregate (future) cancers from healthy (undiagnosed) reference studies. The suggested Primary analysis model combines texture and volumetric density (VBD) into one risk score and improves moderately (non-significant) upon the risk segregation afforded by the individual scores. The Primary analysis further highlighted a sub-category of VDG-2 women as higher risk than density alone suggests. The texture scores were robust across laterality, view and screening populations.

Automated breast ultrasound

Personalised breast cancer screening with ultrasound (US) has been proposed for women with dense breasts and elevated risk factors for developing breast cancer. US is a radiation free technique that is relatively inexpensive. It is known that supplemental handheld ultrasound (HHUS) breast cancer screening
can detect small, early stage invasive cancers that appear to be occult on mammography due to breast density. However HHUS breast cancer screening is operator dependent, difficult to reproduce, time consuming and relatively expensive for screening procedures when performed by radiologists. An alternative to HHUS screening is automated breast ultrasound (ABUS) screening. The ABUS acquisition performed by a trained technician or nurse, it images entire volumes of the breast and stores the entire US volumes enabling temporal comparison.

Because US are the most promising technique for screening of women with dense breasts ASSURE partners focused on the development of US screening protocols to make screening with US more feasible. While introduction of automated scanners brings US screening one step closer to large-scale introduction in screening programs, there is still a big hurdle to overcome: The reading of ABUS scans by radiologists is very time-consuming and, perhaps due to a lack of confidence and experience, the specificity of US screening is rather low. To overcome these limitations, researchers in ASSURE designed a dedicated ABUS workstation for screening. This workstation makes use of advanced features which have the potential to improve radiologist’s performance, both with regard to reading time and quality of the interpretation. In addition, quality assurance tools were developed to ensure that technicians are made aware when image quality is insufficient, allowing them to correct acquisitions and deliver optimal image quality.

Two techniques that are integrated in the workstation are highlighted. The first is a computer aided detection system that was previously developed by the University of Nijmegen and Qview Medical (Lost Altos, CA). This system allows the design of workflows in which radiologists are guided through the complex ultrasound data volumes (six to nine per exam) by the computer, allowing them to focus on relevant areas suspicious for cancer. This is implemented using a 2D navigator image, which serves as a map for the radiologists. By activating highlighted areas in these maps they are led through the 3D data in a natural way, allowing them to inspect and interpret potential abnormalities without distraction. Researchers in Nijmegen also developed new machine learning techniques to aid radiologists with the interpretation of abnormalities once detected. These are intended to help radiologists to better distinguish benign and malignant lesions. This may increase the specificity of US screening.

The second technique developed by researchers in the project aims at helping radiologists to find correspondences. Since there are in general three views per breast, a complete exam includes six data volumes which partly overlap. Large breasts require even more views. In addition, when prior screenings are available, comparisons have to be made regularly with scans in the previous screening exam. When a suspicious finding is detected, radiologists always have to compare the images of this finding to corresponding tissue locations in the prior scan, to determine if the abnormality is new or growing. Thus including the prior scans the evaluation of at least twelve image volumes is required. To aid radiologists with this task, intelligent registration algorithms have been developed and integrated in the screening workstation. These allow radiologists to become more efficient.

To evaluate the ASSURE prototype for US screening several clinical studies were conducted. In one study eight experienced breast imaging specialists from different EU countries reviewed a series of 120 unilateral supplemental ABUS exams. These exams were randomly selected from a large multi-institutional imaging archive. They included 30 randomly selected malignant exams (20 mammography-
negative and 10 mammography-positive) with invasive cancers that were histologically verified. In addition, 30 randomly selected exams with verified benign lesions were included and 60 randomly selected normal cases with ≥ 24 months negative follow up. The specialists read all cases twice in two separate reading sessions which were more than 8 weeks apart. In each session half of the cases were read with the advanced automated detection features and the other half without. In this way the benefit of the new features could be determined. It was found that the reading time was significantly reduced by 15% on average with the novel features. Results also suggest that the system has potential to improve specificity. Overall the system was evaluated as very promising by the readers. It is expected that benefits will become even clearer when it is used prospectively in screening practice, since readers in the study did not have much time to get used to the new workflow.

Figure 7: Screenshot of the developed workstation for ABUS screening. The central image on the lower row is the navigator map. Machine learning is used to provide radiologists with a score on the marked location to support interpretation.

Temporal comparison of automated 3D breast ultrasound (ABUS) examinations is an important task in screening and short term follow up exams. Radiologists perform the task of temporal comparison to assess lesion growth between two consecutive ABUS examinations. Lesion growth is a strong indicator for breast cancer. But ABUS examinations consist of many images and reading is considered relatively time consuming. Smart and fast tools to improve the efficiency of temporal comparison, such as those developed in ASSURE, are very useful for radiologists who read ABUS examinations. To demonstrate this, we performed a reader study to validate the automated location correspondence and lesion segmentation tools that were developed in the project. The temporal comparison tools were integrated into the ASSURE ABUS screening prototype workstation. A special temporal comparison hanging was developed for this purpose. We collected cases that were derived from a prospective clinical trial that was conducted in women that were high at risk for developing breast cancer. We included all 16 cases where a lesion was visible in both the current and the prior ABUS examination. Two experienced reader read all current and prior pairs of lesion twice, once without temporal comparison tool support and once with support of the temporal comparison tools. First the readers needed to find a lesion in a corresponding prior examination. Hereafter, the readers needed to assess if the lesion had grown over time. We recorded the time needed to find a lesion in a corresponding prior ABUS exam. We analyzed reader agreement with the automated growth assessment and the inter-reader agreement between the two readers. Readers performed the task of temporal comparison significantly faster with automated temporal comparison tools (22.0) than without these tools (44.8) (p<.001). However, inter-reader agreement for assessment of lesion volume between the readers became worse when using the segmentation tools. This was due to a lack of quality of the segmentation method and its integration in the prototype. Future work should focus on improving the automated lesion segmentation algorithms and the integration into a clinical workstation.

Breast MRI

Breast Magnetic Resonance Imaging (MRI) is a highly sensitive medical imaging modality that is currently used in breast cancer surveillance of women with a high risk of developing breast cancer. In women with a hereditary high risk of breast cancer development, MRI screening combined with x-ray mammography is
considered cost-effective. MRI may also be useful in personalised screening programs based on breast density stratification in the population of women at an average risk, however MRI is currently considered too costly for breast cancer screening. Furthermore, current MRI standard protocols include the use of intravenous gadolinium contrast-agent injection which is also considered a limitation of MRI.

One of the aims of ASSURE was the development of techniques to increase feasibility and reduce costs of MRI as a screening exam, to enable application of this superior screening modality in a much larger group of women than is currently possible. A current standard protocol of MRI sequences takes between 15-20 minutes per patient. This does not include informing the patient, preparing the intravenous needle and contrast agent and positioning the woman in the MRI scanner. Consequently in most institutes, only two women per hour can be scanned on a single MRI scanner. Decreasing the acquisition time will certainly favor the costs of MRI screening. Time-resolved angiography with stochastic trajectories (TWIST) is an ultrafast high spatiotemporal dynamic contrast enhanced MRI sequence. A TWIST acquisition of two breasts has a diagnostic spatial resolution and simultaneously captures the inflow of contrast-agent in breast lesions at a temporal resolution of 4.3 seconds per time point. A TWIST sequence provides the radiologists information of basic tumor morphology, the time it takes for lesions to enhance (Time to Enhance; TTE) and the relative enhancement of lesions per second (Maximum Slope; MS). Radiologists can differentiate breast lesions better using these dynamic parameters of TWIST than that of a more traditional volumetric interpolated breath-hold examination (VIBE) series. These parameters are useful for both lesion detection and classification and are acquired within 2 minutes (102 seconds). Therefore, TWIST might be suited for fast and accurate breast cancer screening with MRI and less costly.

A step by step screening protocol was developed for both TWIST and traditional VIBE protocols. These were implemented in a prototype MR screening workstation by MeVis Medical Solutions. For evaluation of this system a reader study was conducted to determine the screening performance of radiologists using the system in both traditional MRI protocols and the new screening protocol using TWIST only. A flow diagram of the reading protocol is shown in the figure below.

To select cases for the study we retrospectively searched the Radboudumc electronic patient data archiving system for all women that were enrolled in our MRI screening program for women with an elevated risk of developing breast cancer (lifetime risk of >20%) between 2011 and 2014. We randomly included 120 women with a negatively assessed MRI examination and 2 years of negatively assessed follow-up. Furthermore we included all women with a screen detected biopsied benign lesion (n=53) or a screen detected malignancy (n=31) including invasive breast cancer and ductal carcinoma in situ (DCIS). Available prior examinations (if available) were also included. The ground truth of each scan based on radiology and pathology reports. All MRI examinations that were labelled as normal had at least one negative (BI-RADS 1 or 2) follow up examination. The MRI exams that were labelled as benign and malignant contained lesions that were biopsied and histologically verified by an expert breast pathologist. Two reading sessions were organised with at least a 10 day interval in between to minimise bias caused by any memory effect. In the first session the radiologist screened half of the cases with the traditional MRI protocol (T1 VIBE, DWI, T2) and half of the cases reading TWIST images only. Note that the radiologist did not have access to TWIST during conventional protocol reading and vice versa. In the second reading sessions we swapped the reading modes. In the end, all cases were read once with TWIST and once with a traditional MRI protocol.
Four dedicated breast radiologists participated in the study. We compared the performance of VIBE and TWIST reading using ROC analysis. It was found that results with TWIST alone were as accurate as those with the full VIBE protocol. However, the operating point of the radiologists was slightly different, resulting in a trend towards higher sensitivity in the full diagnostic protocol reading (average 85% vs. 80%) with the diagnostic protocol, but at the cost of lower specificities than in TWIST screening (average 77% vs. 81%). Based on the performance obtained in this study we are of the opinion that TWIST is a very promising MRI sequence that is well suited as an alternative protocol for breast cancer screening. A prospective randomised study should therefore be performed to compare the true screening performance of TWIST with a full diagnostic MRI protocol.

The benefit of the new MRI screening protocol lies in the reduced time of the MRI examination itself. The cost of having an MRI screening program using a full traditional VIBE protocol is approximately 650 euro per hour. Within that hour only 2 women can be screened. We estimated that using a TWIST only protocol would fit at least 6 women in an hour. This would potentially decrease the costs of MRI screening with more than 200 euro per exam. In this study we also showed that the TWIST interpretation time is significantly faster than a full traditional protocol and can be even further reduced when the interpretation is reduced to reading MIPs only, unless a lesion is seen. To introduce a new screening test to a large population, the test should be fast, accurate and relatively cheap. MRI screening using TWIST may qualify for all three criteria.

A limitation of breast MRI is the need for an intravenous contrast agent. This increases the risk of side effects and makes the test less suitable for the general population. Therefore, development of sensitive MRI sequences that don't require contrast is very important, but also highly challenging. In ASSURE an arterial spin labelling sequence for breast imaging was developed. The developed protocol was tested in several volunteers, and a few patients. The figure below shows the best results obtained thus far in a patient with a large cystic breast cancer. Despite the revolutionary nature of the result, as so far a 3D ASL sequence in the breast was non-existent, the image quality of the ASL sequence is not yet at a level where clinical testing becomes relevant. Both the spatial resolution (3.3 * 1.7 * 5 mm), and the amount of artefacts were not acceptable in the current version of the sequence. Hence in terms of clinical viability, the value of ASL at this point in time is non-existent. We are, however, convinced from the results shown above that future developments in this direction may yield clinically highly valuable images.

Stratification and risk models

A number of models have been devised to offer assistance in the task of breast cancer risk assessment. These models fall into two main categories: those which only estimate the probability of a woman carrying a mutation in the high-risk genes BRCA1 or BRCA2, and those which estimate the risk of developing breast cancer over a given timespan, including lifetime. Since the formal mutation analysis of the population is still considered as an expensive and laborious process, the models of the first group aim at identifying women with high probability of carrying one of the previously mentioned mutations. Those women could then be referred for formal genetic testing [2]. While these models are very useful, they are somewhat limited in their scope in the sense that they focus on the identification of the women who carry the mutations of the high-risk genes. The second group of models may be considered broader in scope as
they aim at the assessment of a woman’s risk of developing breast cancer including all available risk factors. Some of these models include an estimation of probability of carrying high-risk gene mutations as a means to estimating overall risk. In the ASSURE project we focused on assessing the risk of developing breast cancer for every woman who attends for breast screening. As a baseline we used the Tyrer-Cuzick model, hereafter abbreviated as simply TC model, which integrates more risk factors than any other existing risk assessment model. Studies suggest that this model outperforms others in terms of its accuracy in predicting the risk of breast cancer.

In the project we investigated the effect of adding density and texture as image-based biomarkers into the TC model via a logistic regression approach. This could only be accomplished using the UK PROCAS datasets since these had the required metadata for the TC risk model available. We performed a meta-analysis that aggregates results of the mammographic risk models based on density scores and adjusted the absolute risk estimate for breast cancer of the Tyrer-Cuzick model for breast density and texture. The main observation of the meta-analysis is that good agreement (high homogeneity) between the estimated odds ratios on the different datasets is demonstrated for VDG1-Tex1, VDG1-Tex2, VDG1-Tex3, and VDG3-Tex1 risk groups. For the other groups; VDG2-Tex2, VDG3-Tex2, and VDG3-Tex3 significant heterogeneity was observed. This is true for either of the texture-based scores (Biomediq and Manchester). This inconsistency in the odds ratios for the latter risk groups could be explained by masking and the relative proportion of interval cancers which varies in the three datasets (PREVENTICON, PROCAS and Copenhagen dataset). A second observation of the analysis is that the pooled estimate from the three individual estimates appears valid in the non-heterogeneous combined density/texture groups and provides an improvement in the precision of the relative risk estimates.

The updated risk scores of the models demonstrate that the models for all three countries included in the ASSURE datasets are similar but not identical. This was to be expected given the similar age-specific cancer incidence rates in the Netherlands, the UK and Denmark. A comparison of the different groups within each risk model also revealed that important differences in absolute risk can be found using mammographic variables and age only.

The experimental results demonstrate that the adjusted Tyrer-Cuzick score assigns consistently more cancers to higher risk, and more controls to lower risk for either of the texture-based methodologies employed (Biomediq and Manchester) compared to the 10-year Tyrer-Cuzick risk of breast cancer. This is a clear indication that the mammographic risk enhanced Tyrer-Cuzick model can provide a better risk stratification tool in a personalised screening paradigm since it identifies more accurately those at high risk of developing breast cancer in the future.

In a final analysis researchers in ASSURE investigated the relative costs and benefits of examples of stratified breast screening programs compared with current practice in two EU Member States (UK and The Netherlands). Key drivers of the relative cost effectiveness of the examples of stratified breast screening programs are identified and results suggest some areas of future research needed to fill gaps in the current evidence base.

Two distinct topics were tackled to complete the economic evaluation of example stratified breast screening strategies. Firstly, a combination of approaches was used to identify the relevant data needed to populate a model that had been conceptualised and built for this work. The approaches used included literature review, expert consultation and, where it was appropriate and feasible, quantitative evidence synthesis of published studies using systematic review and meta-analysis.

Secondly, the assimilated data were then analyzed to generate incremental costs and benefits for each
identified stratified breast screening program compared with current breast screening programs. One-way sensitivity analysis of pre-defined parameters was then used to identify the key drivers of the relative cost-effectiveness of stratified breast screening programs.

A decision-analytic model, including a mathematical model of the natural history of breast cancer and the screening process, was designed to estimate the comparative cost-effectiveness of example stratification protocols. Health benefits were quantified as quality-adjusted life-years (QALYs) gained. A lifetime horizon for costs and benefits was used. Costs were calculated from the healthcare perspective. The model structure and parameter inputs were developed with input from clinical experts within ASSURE and externally. Cost-effectiveness analysis results suggest that stratification protocols have the potential to improve health outcomes with acceptable cost-effectiveness. Key drivers of cost-effectiveness of stratified screening are: choice of cancer growth parameters in the natural history model, screening performance of mammography and US, and the probability of biopsy for recalls and the cost of US. Results were relatively insensitive to probability of recall (if the biopsy rate is fixed) and the costs of stratification itself. Future research needs to address how an optimal stratification protocol should be defined and how risk should be communicated to women in a population-based screening program.

Clinical implementation

Evaluation of effectiveness of personalised screening based on methods developed in ASSURE, and determination of patient’s survival benefit, was outside the scope of this project. However, practical feasibility of stratification using breast density was studied. For this purpose the volumetric breast density software Volpara was installed in two clinics, Institute Jules Bordet in Brussels and Radboud Medical Center in Nijmegen. In both clinics the breast imaging protocol was changed, by offering women with a high breast density a supplemental ABUS exam. In both clinics breast MRI was already offered to women in the highest risk category, including those with the BRCA1 and BRCA2 gene mutations. Thus, effectively this implemented a stratified screening workflow that takes risk and masking into account. In Bordet this was applied in a true screening population. In Radboud Medical Centre the protocol was applied in a clinical setting, with a mixture of symptomatic and asymptomatic patients. In addition to these studies, feasibility of stratified screening was studied in the Dutch DENSE trial led by clinical partner Universitair Medisch Centrum Utrecht in which women in the regular screening program with high breast density are offered MRI. Also in that trial Volpara is used.

At Bordet data was collected from August 2013 to September 2015. Cases were classified according to the type of examination that was performed: Mammography alone or mammography + US, either handheld (HHUS) or ABUS. It was found that of the 8840 screening exams conducted in this period 4179 were categorised with Volpara in the two highest density classes VDG3 and VDG4. Supplemental screening with ultrasound was performed in respectively 86% and 94% of the women in this group. In total seven additional cancers were found that were not seen with mammography.

In Radboud Medical Center a stratified evaluation protocol was introduced for all women who presented at the breast imaging unit in July 2014. This stratified protocol takes density as assessed by the Volpara system into account, using the same software as in the Jules Bordet Institute. However, different from the procedures in Bordet, the Radboudumc breast clinic does not perform regular screening, most patients are either symptomatic, had a personal history of breast cancer, or are at increased risk for the development of breast cancer.

All women who had a Volpara grade 3 or 4 breast density were in theory offered subsequent 3D ultrasound
using the ACUSON S2000 ABUS system (Siemens, Erlangen, Germany). However, to fit this new practice into the routine clinical protocol some exceptions were made: when women were enrolled in the fast-track breast care, biopsy needed to be performed before 11 am to allow same day final diagnosis. If this was jeopardised by the performance of an additional 3D ABUS examination the examination was skipped. This largely explains the large group of women with lesions that underwent mammography alone (and targeted handheld ultrasound + biopsy that is not included in this analysis). In addition, when there was a shortage in staff, 3D ultrasound was omitted if this could not be offered immediately. Also, when women already underwent breast MRI for another indication ABUS was usually not performed.

Evaluation was performed retrospective, to analyses the impact of the implementation of 3D ABUS in routine practice, both in terms of implementation, as well as in terms of cancers detection. We analyzed the frequency of performance of ABUS relative to breast density categories, the frequency of supplemental ABUS based upon density alone, and the additional yield of benign and malignant abnormalities.

In total 4163 women were analyzed between July 2014 and September 2015. For 3932 of those a Volpara score was available. In total 270 cancers were assessed and 240 benign lesions were biopsied. ABUS scans were performed in 920 patients who also underwent mammography. In table 11 the results regarding implementation are shown. ABUS was performed in the target group in only 33% of the cases. This clearly shows that, even though the indications were strict, actual implementation was hard. While this may be partly explained by the screening of women who did undergo breast MRI, it was evident that lack of routine and shortage of staff played especially in the beginning a major role in the non-performance of ABUS scans. In addition, however, some of the 3D ABUS scans were performed at the discretion of the evaluating radiologists, while this was not indicated according to measured breast density. This implies that some of the 3D ultrasound acquisitions were performed to resolve imaging or clinical findings rather than for supplemental evaluation of dense breast tissue. We must therefore assume that in a similar fraction (6.4%) of the VDG 3 and 4 groups the 3D ultrasound examinations were likewise performed for clinical indications, rather than supplemental evaluation. This implies that approximately 408 women in the VDG 3 group underwent supplemental ABUS based upon density alone, and 248 women in the VDG 4 group; in total accounting for 656 supplemental evaluations for density alone.

In total 510 lesions were biopsied based upon clinical and imaging findings, 270 were malignant, 240 were benign. For 407 exams with lesions a Volpara score was available (195 malignant lesions and 212 benign lesions). For 396 lesions the reporting was clear enough to discern the method of detection. It was found that six women presented with a cancer that was occult on mammography, but was detected on ABUS. In addition 15 benign biopsied lesions were only seen on ABUS; which yields a positive predictive value of ABUS induced biopsies of 29%.

However, clinical findings and/or other imaging modalities did play a role in the decision to biopsy for many of these lesions. Since two of the six patients were symptomatic, and 2 also underwent MRI, on which the cancer was also detected, the added yield of ABUS only was less than six. Nevertheless, two larger cancers in women who underwent follow-up screening for a personal history of breast cancer were detected which would otherwise have been missed. Results can be translated to an additional cancer detection rate of 3 per 1000 supplemental evaluations, which is conform other results published in literature.

The outcomes of the retrospective analysis of Bordet data, Radboud data, along with those of the DENSE trial, showed that it is practically feasible to implement a personalised screening procedure including stratification based on automated density measurements, adding US and/or MRI to the regular mammography exam. However, it is too early to make any definitive statement about effectiveness of this
procedure but the figures we gathered tend to suggest that they could lead to an increased early tumor detection rate but also to a lower rate of negative biopsies compared to diagnosis based on mammography alone.

Potential Impact:
The ASSURE consortium brings together many years of experience and expertise in research in the field of image-based medicine as well as a substantial track record of exploitation actions aiming at transforming research results into successful commercial products. In particular in the field of breast cancer imaging, several partners of the consortium have achieved commercial successes from joint publicly funded research actions. For instance, FME (formerly MeVis Research) and RUNMC participated in the two European research projects SCREEN and SCREEN Trial, in which a prototype of a workstation software for digital mammography reading was developed and its suitability for population-based breast cancer screening programs demonstrated. The resulting software prototype was subsequently commercialised by MMS and formed the basis of today’s state-of-the-art software products for high-throughput digital mammography screening. Likewise the SMEs and ASSURE partners MTKN, Biomediq and MDRI have picked up early results from academic research in the past and have transformed these technologies into innovative commercial products.

The four SMEs in the ASSURE project have complementary business foci which together cover all thematic fields of research addressed in the consortium’s work program. MTKN has a portfolio of software products for automated breast density measurements and imaging process analytics. The research carried out by the ASSURE consortium in the field for breast density quantification enabled significant potential to improve the quality of existing and to form the basis of new related software products. MeVis Medical Solutions AG is already today manufacturer of a spectrum of dedicated software applications for early detection and diagnosis of breast cancer with mammography, tomosynthesis, MRI and automated 3D ultrasound imaging. The research results contributed to the competitiveness and success of these products. With its software technology for automated quality assurance in medical imaging, the start-up company MDRI is developing a novel product and is opening up a completely new market segment. The results in the field of risk stratification and cost-effectiveness analyses and the results from the clinical evaluation generated additional market demand for new innovative software tools and workflows for personalised breast cancer screening and are therefore important contributions and enablers for the introduction of new products based on technologies developed in ASSURE.

The SMEs have developed and established a range of distribution channels which can be utilised for the commercial exploitation of the ASSURE foreground. These channels comprise longstanding OEM partnerships with leading and globally operating manufacturers of healthcare technology as well as direct access to clinical end customers through own sales and marketing organizations. Also the proportion of value-chains implemented by the partnering SMEs varies from licensing of technology and IP to third parties, through development of comprehensive white-label software applications to development, regulatory clearance, direct marketing and maintenance of commercial end products under own brands. In order to promote a broad commercial exploitation of the entire foreground generated by the ASSURE consortium, all partners have agreed on a Consortium Agreement which, among other things, sets forth provisions for comprehensive dissemination and exploitation of foreground. These provisions are geared to the regulations in the Grant Agreement Article II.26. – Article II.29 and aim at fostering and balancing collaborative work through exchange of relevant background and foreground, broad dissemination of results in the scientific communities as described in the joint dissemination plan as well as effective
protection of IP through patents and exploitation of research results with commercial potential.

In addition to the Consortium Agreement several partners have jointly signed complementary collaboration agreements or agreements with third parties to expedite the achievement of the set research and commercial exploitation objectives. The ASSURE partners MMS and RUNMC have signed a Memorandum of Understanding with the affiliated partner MeVis BreastCare GmbH & Co. KG, Germany and the US-based start-up QView Medical, CA. The agreement enables the signees to expand their collaboration in the field of CAD for automated 3D ultrasound and to align related activities with the ASSURE work program. It forms also basis for further negotiations between the signees and Siemens Healthcare aiming at commercializing the CAD algorithms as part of the existing Siemens product Synge. Ultrasound Breast Analysis (subs), which is developed as a white-label application by the affiliated partner MeVis BreastCare. Similarly, MTKN and Biomediq have signed a bilateral agreement to expand their collaboration in the field of breast density quantification beyond the stipulation set forth in the ASSURE Consortium Agreement.

The composition of the consortium and in particular the diverse business models of the partnering SMEs allow for a spectrum of strategies for commercial exploitation of the foreground generated within the ASSURE program. The strengthening of existing commercial products with new software technologies developed in ASSURE and the utilization of established sales and marketing relations with globally operating manufacturers of healthcare equipment enable the partners to significantly shorten time-to-market and to have a positive impact on clinical practice as well as on the partner’s business already during the life time of the project. Nonetheless, the consortium also possesses proven experiences in developing alternative exploitation strategies based, e.g. on the introduction of new commercial products or on the foundation of new companies.

All SMEs have installed measures for IPR protection and timely identification of foreground of commercial relevance. These measures have already resulted in the filing of several patents and in the exploitation of foreground as part of new products. Additionally, discussions and negotiations with third parties and potential business partners, in particular with leading technology providers in the women’s imaging sector, have been started and will be continued after the project life time. The information gained from these discussions served the ASSURE consortium also as input for the alignment of its work program and research objectives with latest market demands.

The strategies for the commercial exploitation of the results generated by the ASSURE consortium primarily depend on the existing business models of the SMEs, which were the driving force in this matter. Nevertheless, in particular the academic partners were at the same time continuously seeking non-commercial opportunities for utilizing know-how and tools developed in ASSURE for supporting research outside the immediate scope of ASSURE. The following sections outline the individual business models of the SMEs and describe how each partner utilises the achieved results for commercial or non-commercial purposes.

MeVis Medical Solutions AG
MeVis Medical Solution (MMS) made extensive use of the knowledge, algorithms and software components developed by the ASSURE consortium. Major goal was to safeguard the market positions of the existing women’s health imaging products of MMS. To constantly monitor the level of maturity and to assure a timely commercialization of suitable ASSURE foreground, MMS established communication processes between the ASSURE team and the product development units at MMS and its joint-venture MeVis BreastCare GmbH & Co. KG.

MeVis Medical Solutions AG was founded in 1997 as a spin-off of the non-commercial research institute
MeVis Research gGmbH (today Fraunhofer MEVIS). From early on, MMS developed a strong focus for the segment of radiologic software for women's health imaging. By means of the knowledge and experience gained in research projects funded by the German government and European Commission, MMS became one of the world's leading independent producers of software solutions in this market segment.

Software products developed by MMS are currently exclusively distributed through OEMs partnerships. Longstanding business relations with major healthcare providers such as Siemens Healthcare, Philips, Toshiba and Hologic have enabled MMS to offer its products to customers in the USA, Europe and Asia. With a global install base of several thousand software installations in 2013, software products developed by MMS capture a significant share of the corresponding segments in all major markets. MMS itself has longstanding OEM partnerships with Invivo Corporation (Philips Healthcare), Vital Images (Toshiba) and Hologic Inc., which belongs to the major technology providers for women's health care. Within these partnerships, MMS delivers, among other software products, advanced software solutions for early breast cancer detection and diagnosis with digital mammography, tomosynthesis and dynamic contrast-enhanced MRI.

MMS expects that the ASSURE results will substantially strengthen its products portfolio and potentially open up new business opportunities. In recent years, automated 3D ultrasound has received much attention as a novel non-radiating breast imaging modality which is considered to bear potential for cancer screening. Yet, the long reading time for the 3D image volumes prevents a broader utilization of the modality today. Since the ASSURE consortium was able to demonstrate that the reading time can be considerably reduced with CAD tools and dedicated reading workflows, it provides valuable technologies and new information serving as input for a reassessment of the role automated 3D ultrasound plays in breast cancer screening. The early integration of corresponding novel software tools into the existing product considerably reduced time-to-market and enables MMS to address the resulting market demand in a timely fashion. In a similar way, MMS evaluates that the research carried out in the field of MR-based imaging provides new data motivating the use of MRI for screening larger cohorts for breast cancer. In general, the software tools developed in ASSURE are complementary to the scope of functions of the existing MMS products and are excellent starting points for product development efforts addressing potential new market demands. While the integration of breast density quantification tools into MMS reading applications is not part of the ASSURE work program, MMS and MTKN are investigating potential opportunities for joint business.

Matakina UK Limited

Matakina is an SME in the medical devices industry of the healthcare sector. Matakina’s current primary scope of business is the development of image analysis software for in-vivo quantification of breast tissue. The flagship product is Volpara, a software tool which measures volumetric breast density for the automated analysis of mammograms. The scientific technology underlying this product forms the foundation of the future product lines, including dose measurement and minimization, tomosynthesis reconstruction and optimal display, computer aided diagnosis and image registration. The Volpara technology resulted from original research from Oxford University, by founders Professor Sir Michael Brady, then BP Professor of Information Engineering, and Dr Ralph Highnam, whom published the work in the 1999 monograph ‘Mammographic Image Analysis’. Since this time the technology has undergone countless developments and refinements, one of particular significance being the "relative physics" methodology presented by van Engeland and Professor Nico Karssemeijer (also a company co-founder and ASSURE partner) from Radboud University in Nijmegen. Matakina therefore has a lifetime history of...
commercialization of novel academic research, originating from the very roots of its inception. Founding director, Professor Sir Brady is a serial entrepreneur, having started a number of other companies in addition to Matakina, in such areas as image registration/fusion (Mirada Medical Ltd), and most recently liver disease scanning using MRI (Perspectum Diagnostics Ltd).

Since 2009 Matakina, through its wholly owned sales arm, Volpara Solutions, markets and sells its FDA and CE approved Volpara software family, Density, Dose and Analytics, through a number of channels: direct to customers via its own world-wide sales force (direct being the predominant model in the US); via original equipment manufacturers (iCAD for example); and through a network of local distributors (the predominant model in the EMEA and APAC regions). Work is currently underway to expand the current implementation models to include delivery of the Volpara software suite via The Cloud, using such technologies as the Microsoft Azure platform.

The ASSURE project has contributed to the forward progression of Matakina in a number of ways. Firstly through the validation of the underlying technology of Volpara Density, and verification of the associated clinical workflows, for example stratification of dense breast women for adjunctive imaging examination using automated whole breast ultrasound (currently being utilised by several ASSURE partners clinically). The extensive databases of screening mammograms, enriched by the additional extensive meta-data collected beyond that normally found in current clinical practice, made available by the various clinical partners facilitated the publication of Volpara risk correlations in opinion setting peer reviewed journals.

Secondly, Matakina envisions significant progression through the securing and commercialization of IP developed in ASSURE. Matakina has a dedicated IP manager whom ensures that novel inventions arising from the work of the company are secured by patent or copyright protection. Thus far two provisional patents have been filed covering inventions developed by Matakina in the course of its work on the ASSURE project. The IP manager is also responsible for in-licensing new technology to augment the feature set of existing products, or to enhance the company’s overall product portfolio. The ASSURE project and its associated partners are considered prime territory for such in-licensing. Particular attention is currently being focused on the texture quantification metrics being developed by several of the partners (both academic and commercial) within the project for possible licensing and inclusion in the flagship Volpara Density product to supplement the volumetric breast density reading it currently delivers to clinicians. Similarly, the work on individual patient risk models and quantification of masking risk, being conducted by the other partners is of interest for augmenting the current product line, and delivering to our existing customer base as enhanced functionality of their existing purchase of our clinical server system.

Biomed IQ AS

Biomediq A/S is a Danish SME performing contract research for the pharmacological industry and contract research organizations performing clinical trials in which quantification of medical images are involved. They market validated, automatic and semi-automatic analyses of knee MRI for scoring of cartilage quantity (volume, thickness) and quality (surface smoothness, homogeneity, congruity); and bone structure in relation to osteoarthritis; analyses of mammograms for breast cancer risk; analyses of lateral spine x-rays for fracture and fracture risk quantification; analyses of lumbar lateral x-rays for abdominal aortic calcification scoring; brain MRI scoring of morphometry, structure, and texture for relation to neurodegenerative diseases.

Biomediq A/S strategy in the breast cancer risk analysis area is to market a software device for analysis of mammograms for planimetric density and planimetric texture scoring. This device will, according to research done in ASSURE and the DNATF funded project “Personalised Breast Cancer Screening” add
considerably to breast cancer risk segregation compared to volumetric density alone. The business model is to sell licenses including hardware to clinics providing density/texture scores for raw digital mammograms. It is being explored if this may be done in conjunction with Matakina. CE-marking and FDA clearance is being actively pursued for marketing in EU and US. The results of ASSURE show that mammogram-based risk stratification for personalization of screening has a positive cost benefit profile. This may be the major scientific hallmark generating interest for Biomediq’s mammogram-based risk analysis. At a later stage, Biomediq also hopes to make new versions including temporal changes of density/texture in the risk analysis based on D2.4. Furthermore, a product relating to risk of masking of cancers based on D1.8 is aimed at.

Medical Imaging Research Institute

Mediri GmbH is a private research institution dedicated to developments in medical imaging, technological transfer to clinics and support services for image based clinical trials. Mediri was founded in 2004 and since then, several research activities have been exploited commercially.

Two MR compatible research prototypes for organ tracking and motion correction based on ultrasound imaging have been developed: Sonoplan and Sonoplan II. The idea of Sonoplan has been patented as “EP2358276: 3D motion detection and correction by object tracking in ultrasound images”. Additionally, Sonoplan has been registered as trademark.

Apart from the software development Sonoplan, a MR imaging sequence for contrast agent-less perfusion imaging (arterial spin labeling) called ASL 3D-GRASE (product version) was developed. This ASL 3D-GRASE sequence has been licensed to Siemens. Also, dedicated post-processing software for ASL perfusion quantification was developed.

Today, Mediri supports image based clinical trials for Merck, Novartis, Biogen, Tetec and others. In these trials, image data management and workflow design is being provided as well as support with automated image processing tools based on a proprietary software technology of Mediri. This technology forms also the basis for mediri’s automated image quality assurance (AQUA) software. AQUA is used in several clinical trials, mainly for the quality assurance in MR imaging of the brain or spine.

In the ASSURE project, mediri is mainly involved in the development of AQUA tools for automated breast ultrasound (ABUS) and breast MR images. As ABUS and breast MR imaging are new fields of research for mediri, this project is an important contributor to the extension of mediri’s portfolio of imaging services. It was expected that software prototypes for AQUA on ABUS and breast MR imaging would be developed. A detailed analysis of the current demand for such tools with respect to breast cancer screening showed, however, that ABUS AQUA tools would be of much higher interest than AQUA for DCE breast MRI. Thus, an ABUS AQUA prototype was implemented and tested in breast cancer screening environment allowing further insight to the related clinical workflows and their specific requirements regarding quality assurance. The implementation of AQUA modules for breast imaging into the existing in-house image processing and workflow management engine MIRIAM opens new perspectives and opportunities in the area of clinical trial support. Apart from that, mediri will profit from licensing specific AQUA software modules to research partners and other interested parties in the future.

Fraunhofer MEVIS

The methods developed at Fraunhofer MEVIS provide mid-term options for commercialization. The developed methods had a special focus on screening and follow up evaluation in MRI, i.e. by facilitating follow up by linking lesions from older exams to the most recent, shortening the overall examination time, or potentially allowing to avoid the usage of contrast agents. These will be of high interest once clinical studies have been conducted to show the potentials of these new methods. Potential customers are
manufacturers of clinical software and MRI devices.

The methods developed in ASSURE are still subject of research. A pilot study on contrast agent less sequences (ASL and HiSS) yielded one case showing a clear ASL signal from a breast tumor. This tumor was also investigated in HiSS and the data was compared to conventional contrast enhanced MRI. The work on contrast agent less sequences will be continued, especially the collaboration with RUNMC. Since there was a software version update in Nijmegen it will be necessary to update the sequences in Nijmegen to allow further research. Ones this is accomplished, we will continue researching on these promising sequences. With more clinical evidence, these sequences can become of interest to large MRI device manufacturers for the sequences and for the reconstruction software.

A novel software workflow for the linking of lesions in current and prior studies was implemented. It allows a more accurate linking because of the implemented template matching developed by FME. The template matching was delivered to MMS and FEM helped with the implementation in the professional workstation developed at MMS. This technology might be directly interesting to vendors of breast MRI workstation. Thirdly, in parallel to the MRI reading workstation developed by MMS, FEM developed a fast experimental screening viewer with minimal interaction with the radiologist and a pre caching of cases allowing an instantaneous loading of the next cases for a large set of screening MRI datasets. This prototype will be used to support clinical trials on breast MRI and might also become of interest to screening workstation developers.

The University of Manchester
The University of Manchester became the largest single site university in the UK in 2005 with the merger of the Victoria University of Manchester and the University of Manchester Institute of Science and Technology (UMIST). Currently 38th in the world rankings, it has an ambitious program of development to become one of the top 25 universities in the world by 2015. Development is occurring University wide and cancer is one of two areas selected for rapid development. It has significant existing activities in cancer research within the Faculties of Medical and Human Sciences and Life Sciences. Its Institute of Population Health is one of six new institutes in the Faculty of Medical and Human Sciences. These were created to enable the University of Manchester to reach its full potential as an internationally esteemed center for research and education in medical and human sciences, and to translate that expertise into improved health and wellbeing for people locally, nationally and internationally.

While it is unlikely that the new know-how generated by the Manchester Centre for Health Economics within the ASSURE program bears significant potential for commercial exploitation by the University of Manchester, it may provide important information and evidence for promoting the clinical, and therewith commercial, value of the software technologies developed by other ASSURE partners. Therefore, the main ways in which the results from the economic analysis conducted as part of the ASSURE project can be exploited is in terms of (i) informing new national screening policies and (ii) providing early evidence of the potential costs and benefits of risk and density based stratified screening programs to feed into the design of subsequent ‘follow-up’ research projects. The economic analysis in ASSURE which provide information about the relative costs and benefits of risk and density based stratified breast screening programs in three exemplar EU member states. These analyses will show the key drivers of cost-effectiveness and also the key gaps in the evidence base and areas of uncertainty. Knowing these key areas of uncertainty can target the future research necessary to inform these evidence gaps.

Radboud University Nijmegen
The Radboud University Medical Center is uniquely positioned in the emerging Euregio and Dutch healthcare infrastructure to play a leading role in the new healthcare paradigm of prediction, prevention
and personalised medicine. The center has an impressive infrastructure comprising state-of-the-art technology platforms and research facilities. The center is particularly strong in medical imaging research. The department of Radiology and Nuclear Medicine employs more than hundred researchers, most of them with a focus on oncology. Many projects are carried out in collaboration with industry, which underlines the ambition of the center to play a role in the translation of research results to clinical imaging applications used in everyday practice.

Improvement of the detection, diagnosis and treatment of breast cancer by advanced imaging applications is one of the fields in which the Medical Center excels. Currently, the breast imaging research group has thirteen researchers working on a variety of topics. Seven companies are involved in this research, including the four SMEs of the ASSURE project.

In the ASSURE project, the primary aim of the Medical Centre was to make research results available for exploitation by the commercial partners in the project and to researchers in the field, to be used in future projects. The Medical Centre does not have plans for direct commercial exploitation on its own behalf since it does not see product development as its role. If valuable knowledge results in patents the University intends to make a royalty agreement with partners or spinoffs, and use potential revenues for funding further research.

To fund its breast imaging research program in the future, the University has to make sure that it keeps its unique knowledge and expertise in breast imaging up to date. Research in the ASSURE has helped RUNMC to do this, making the center an attractive partner for future collaborative research projects in this field. The ASSURE project has strengthened RUNMC’s position as a leading academic institution by means of the scientific publications, the expansion of knowledge, and the generation of structured image databases in the field of breast cancer research. This further strengthening of our positions has further improved visibility of our research group, and has improved RUNMC’s position to obtain external funding.

In the ASSURE project, the technology for breast screening with whole breast ultrasound is an important topic in which Nijmegen is involved. This research builds on an existing cooperation between Nijmegen and the company QView Medical in California, which is not directly involved in ASSURE. However, since the start of the project a strong synergy was developed between QView Medical and MMS and the companies are currently collaborating. This collaboration continues to open up great opportunities for the ASSURE research to apply, evaluate and further develop CAD for automated breast ultrasound in a clinical environment. For the University it has considerably strengthened the relation with both MMS and QView Medical. QView Medical is currently funding breast cancer research at RUNMC.

The availability of new imaging technology in the radiology department makes the medical center more attractive for patients and allows the department to maintain its position as a leading center for management of breast cancer patients. Automated breast density measurements using Volpara were introduced as part of the ASSURE project and routine evaluation of patients with high breast density with automated 3D ultrasound has started. This is a good example of how personalised healthcare is facilitated by ASSURE, and it allows us to evaluate new procedures developed in the project.

In the first year of ASSURE, two of the founders of Matakina developed plans to start a spin-off company in Nijmegen for development of new technology for computer aided detection of breast cancer in screening mammograms. After successful negotiations the company ScreenPoint Medical was founded. Though not directly based on results of ASSURE, the collaboration in the ASSURE project was definitely a factor that helped to establish this spin-off.

Recently RUNMC together with ASSURE’s SME partner BMIQ was awarded a Eurostars grant to continue research in breast cancer CAD. In the project E - IBSCREEN “Intelligent, automated and cost-
effective breast cancer screening”. Both partners, together with the university and university hospital of Copenhagen, and startup company Screenpoint will continue and further improve work on breast cancer CAD.

University Medical Center Utrecht

Personalised cancer care, for breast cancer patients in particular, is one of the priority programs of the University Medical Centre Utrecht (UMCU). Researchers of the Cancer Epidemiology group of the Julius Centre for Health Sciences and Primary Care, a division of the UMCU, play a key role in this program and in the UMCU Cancer Centre. The research focus of this group of twenty researchers is on the prevention, early detection and diagnosis of breast cancer. Researchers of this group have been involved in the set-up and evaluation of one of the first breast cancer screening programs in the Netherlands (1975) and within this framework there is a consolidated research line on breast density for over 10 years now. The Cancer Epidemiology group is closely collaborating with the Radiology Department of the UMCU. Together they coordinate the DENSE (Dense tissue and Early breast Neoplasm ScrEening) trial, a large multicentre randomised controlled trial (>30,000 women) investigating the additional value of MRI for women with extremely dense breasts in the population based breast cancer screening program in the Netherlands.

UMCU’s contribution to the ASSURE project is epidemiological analysis of the various breast density quantification measures in relation to risk of breast cancer, and construction and validation of the risk prediction models. UMCU acts as a clinical partner. The results of ASSURE are of great importance to the DENSE trial, described above and together ASSURE and DENSE will give important input to the Dutch and other European screening programs.

Furthermore, UMCU will use the breast density measures showing strong and robust risk estimates in other research projects to:
- study determinants of these breast density measures, in order to identify new breast cancer risk factors,
- study these breast density measures in relation to risk of specific breast cancer subtypes,
- find biologic markers in blood, nipple fluid or tissue that correlate with these new breast measures, in order to obtain more insight into the mechanism by which risk is increased, and
- identify women with increased risk of a (missed) breast cancer to include them in breast cancer detection and prevention trials.

Institut Jules Bordet

Institut Jules Bordet participates in the ASSURE projects as clinical partner. Its main focus is to consult other partners and to support the clinical evaluation of the new software tools developed in ASSURE.

University of Girona

The Computer Vision and Robotics Group researchers have experience in developing methods for mass detection in mammography incorporating both lesion shape and density information. Moreover, they also have expertise on temporal and contra-lateral mammographic image comparison based on image registration and region matching, and have proposed several works on model-based and probabilistic image segmentation applied to breast MRI and ultrasound imaging. Therefore, the use of ASSURE results in partial developments of Computer-Aided Diagnosis systems is highly feasible, especially when using multimodal imaging techniques. Tuning those CAD systems according to the stratified risk model is expected to improve their performance.

List of Websites:

www.assure-project.eu