Measurement challenge: protocol for international case–control comparison of mammographic measures that predict breast cancer risk

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BMJ Open  Measurement challenge: protocol for international case–control comparison of mammographic measures that predict breast cancer risk

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ABSTRACT

Introduction For women of the same age and body mass index, increased mammographic density is one of the strongest predictors of breast cancer risk. There are multiple methods of measuring mammographic density and other features in a mammogram that could potentially be used in a screening setting to identify and target women at high risk of developing breast cancer. However, it is unclear which measurement method provides the strongest predictor of breast cancer risk.

Methods and analysis The measurement challenge has been established as an international resource to offer a common set of anonymised mammogram images for measurement and analysis. To date, full field digital mammogram images and core data from 1650 cases and 1929 controls from five countries have been collated. The measurement challenge is an ongoing collaboration and we are continuing to expand the resource to include additional image sets across different populations (from contributors) and to compare additional measurement methods (by challengers). The intended use of the measurement challenge resource is for refinement and validation of new and existing mammographic measurement methods. The measurement challenge resource provides a standardised dataset of mammographic images and core data that enables investigators to directly compare methods of measuring mammographic density or other mammographic features in case/control sets of both raw and processed images, for the purposes of the comparing their predictions of breast cancer risk.

Ethics and dissemination Challengers and contributors are required to enter a Research Collaboration Agreement with the University of Melbourne prior to participation in the measurement challenge. The Challenge database of collated data and images are stored in a secure data repository at the University of Melbourne. Ethics approval for the measurement challenge is held at University of Melbourne (HREC ID 0931343.3).

Strengths and limitations of this study

► The measurement challenge is a unique annotated resource that enables timely and prompt comparison of different mammographic measurement methods applied to full field digital mammogram images, and thereby robust assessment of which measurement method provides the ‘best’ predictor of breast cancer risk within different screening settings.

► The measurement challenge currently includes anonymised mammographic images and core data from 1650 cases and 1929 controls from five different sample populations.

► The measurement challenge is an ongoing collaboration and we are continuing to expand the resource to include additional image sets across different populations (from contributors) and to apply additional measurement methods (by challengers).

► The measurement challenge provides a much-needed standardised dataset with which to refine and assess new or existing mammographic measurement methods but is currently underpowered to examine the association between mammographic measures and breast cancer risk in non-European/Caucasian populations.

INTRODUCTION

Mammograms are the current standard in population-based screening for breast cancer in women aged 40 or above. For women of the same age and body mass index (BMI), increased mammographic density is one of the strongest predictors of breast cancer risk.1–3 There are multiple methods of measuring mammographic density and other features of a mammogram that could potentially be used in a screening setting.
to identify and target women at high risk of developing breast cancer. However, it is unclear which measurement method provides the strongest predictor of breast cancer risk.

The measurement challenge is an international resource that offers a common set of raw and/or processed full field digital mammograms for measurement and analysis. By providing an annotated dataset of mammogram images and core data, this resource will enable investigators to directly compare methods of measuring mammographic density or other mammographic features as predictors of breast cancer risk.

Initiated in 2016, the measurement challenge has collated full field digital mammograms images and core data from 1650 cases and 1929 controls from five countries (Australia, Malaysia, Norway, UK and the USA) to date. Images have been randomly divided to form a training set and a validation set for challenge measurement. Further contributions are welcomed.

There are currently eight challenger research groups who have applied measurement methods to the resource dataset. These include fully automated approaches (ie, AutoDensity, BIOMEDIQ, DeepRisk, Laboratory for Individualized Breast Radiodensity Assessment (LIBRA), MMTEXT, OpenBreast V.1.0 and VolparaDensity) and semiautomated methods (ie, Cumulus, including AltoCumulus and CirroCumulus).

The measurement challenge is an ongoing collaboration and we are continuing to expand the resource to include additional image sets across different populations and to apply additional measurement methods. More image sets are needed to improve statistical power and provide sufficient data to address incompatibilities between measurement methods and image type and/or manufacturer.

The potential benefit of pooling and standardising mammographic images from different populations includes providing a large set of images with which to refine and assess new or existing mammographic measurement methods. We anticipate that the measurement challenge will become a unique annotated resource for timely and prompt comparison of different mammographic measurement methods with the aim of identifying mammographic measures that best predict breast cancer risk in different screening settings. Given the increased measurement and reporting of mammographic density internationally, identifying the measurement method/s that best discriminates women who will or will not be diagnosed with breast cancer in the future could substantially improve existing risk prediction models and ultimately help improve the efficiency and effectiveness of screening programs by triaging women according to risk. The cost and ease of implementing routine mammographic measurement in local clinical settings would depend on the requirements and idiosyncrasies of each screening programmes.

METHODS AND ANALYSIS

As part of the first phase of the measurement challenge, full field digital mammogram images and core data from 1650 cases and 1929 controls have been collated. The resource has been collated from five contributing studies in Australia, Malaysia, Norway, the UK and the USA (henceforth contributors). Both contributors of case–control image sets and investigators interested in applying their measurement methods (henceforth challengers) are required to enter a Research Collaboration Agreement with The University of Melbourne prior to participation in the measurement challenge.

Data are obtained from existing epidemiological case–control studies or nested case–control studies. For the former, diagnostic or prediagnostic mammograms are obtained for cases with comparable mammograms obtained for controls. For nested case–control studies, mammograms taken at the time of entry into the cohort are used and incident cancers diagnosed within 1 year after the baseline screen negative mammogram are excluded to avoid masking bias or false negatives. Control selection differed slightly for each study (references provided in table 1); at a minimum, controls were frequency matched for age post hoc.

Table 1 describes the mammographic image data available by contributor, to date. Both raw and processed images are available for 1003 cases and 1283 controls; processed images are available for 1650 cases and 1929 controls. Core participant data consist of year at mammogram, year of birth, year of interview, BMI at mammogram and ethnicity. For breast cancer cases, breast cancer laterality and year of diagnosis is also available. Additional image data include laterality, view and mammography manufacturer.

Anonymised mammographic images and core data are available to challengers interested in applying their measurement methods in two sets. Images from each source are randomly divided (50:50) in two (stratified by case–control status) and assigned to a ‘test set’ or a ‘validation set’. The test set is intended for use in refining new measurement methods or for training purposes, and the corresponding core data includes breast cancer status. It is made available to all challengers for a specified period of time. The validation set is provided for measurement validation and the corresponding core data does not include any information regarding breast cancer status. Both sets of images are securely transferred to challengers for the measurement using their method (multiple methods are permitted).

Thus far, eight challengers from Australia, Denmark, Finland, Malaysia, Norway, the UK and the USA have accessed the measurement challenge core data. Measurement methods include AutoDensity, BIOMEDIQ, Cumulus (Sunnybrook Women’s Hospital, Toronto Canada), including AltoCumulus and Cirro-Cumulus, DeepRisk, LIBRA, MMTEXT, OpenBreast V.1.0 and VolparaDensity. AutoDensity automatically preprocesses images by identifying the breast area using...
Table 1 Characteristics of available measurement challenge images and data

<table>
<thead>
<tr>
<th>Country (where images were sourced)</th>
<th>Study design</th>
<th>No case/controls</th>
<th>Ethnic majority</th>
<th>Mean age (SD)</th>
<th>Mean BMI (SD)</th>
<th>Image type</th>
<th>Mammogram view</th>
<th>Machine manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Nested Case/control</td>
<td>464/463</td>
<td>European</td>
<td>62.9 (7.1)</td>
<td>27.3 (5.4)</td>
<td>P</td>
<td>CC, MLO</td>
<td>Fuji, Hologic, Siemens</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Case/control</td>
<td>202/202</td>
<td>Chinese</td>
<td>50.9 (11.5)</td>
<td>23.4 (3.8)</td>
<td>R, P</td>
<td>CC, MLO</td>
<td>Hologic</td>
</tr>
<tr>
<td>UK</td>
<td>Case/control</td>
<td>403/683</td>
<td>European</td>
<td>62.1 (9.8)</td>
<td>26.2 (5.4)</td>
<td>R, P</td>
<td>CC</td>
<td>GE</td>
</tr>
<tr>
<td>USA</td>
<td>Case/control</td>
<td>398/398</td>
<td>European</td>
<td>55.1 (10.9)</td>
<td>27.8 (6.3)</td>
<td>R, P</td>
<td>CC, MLO</td>
<td>GE, Hologic</td>
</tr>
<tr>
<td>Scandinavia</td>
<td>Nested Case/control</td>
<td>183/183</td>
<td>European</td>
<td>59.7 (6.2)</td>
<td>24.7 (3.4)</td>
<td>P</td>
<td>CC, MLO</td>
<td>GE</td>
</tr>
<tr>
<td>Combined (all data)</td>
<td></td>
<td>1650/1929</td>
<td>European</td>
<td>59.3 (10.2)</td>
<td>26.2 (5.3)</td>
<td>R, P</td>
<td>CC, MLO</td>
<td>GE, Hologic</td>
</tr>
</tbody>
</table>

CC, craniocaudal; GE, general electric; MLO, mediolateral-oblique; P, processed image; R, raw image.

Overview of analysis protocol

To prepare the data for analysis, we exclude images of the affected breast for all cases. We also ensure that age distributions are similar across cases and controls. Age frequency matching is performed randomly within rolling 5-year intervals and separately by each image type. For most women, four mammograms are available (ie, both sides and views). If multiple measurements have been submitted for the same person, we average these separately for each image type. The VolparaDensity challenge has provided a specific custom average which is separately submitted for each image type. The VolparaDensity algorithm has been run using the same parameters for all images.

All challenges are required to provide their measurements from the validation set for statistical analysis. A method to assess and compare the performance of each measurement method is described in the Overview of analysis protocol below and will be completed by a statistician with no vested interest in the outcome.

Statistical criteria for assessing and comparing performance of each measurement method are described in the Overview of analysis protocol below and will be completed by a statistician with no vested interest in the outcome.

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used. Details regarding its calculation can be provided on
request.
Not all challengers can measure each image due to
image type and/or quality; measured proportions will be
reported by technique. A complete dataset that contains
all images that every challenger can measure is used for
the principal analysis. In addition, we also run all calcu-
lations individually for each challenger using all images
that this specific challenger submitted.

Logistic regression is used to estimate the association
between the mammographic measure and breast cancer
risk for each method, stratifying by image type (raw or
processed). Adjustment for covariates includes age, BMI,
machine manufacturer and source.
Box-Cox transformations are used to better approxi-
mate normality,
\[ f(x) = \frac{x^\lambda - 1}{\lambda} \text{ if } \lambda \neq 0 \]
\[ \log(x) \text{ if } \lambda = 0 \]

where \( x \) is the mammographic measurement and \( \lambda \)
is chosen to maximise the profile likelihood of a linear
model of \( x \). The value of \( \lambda \) obtained and used for transfor-
mation will be reported for each measurement method.

We calculate standard ORs per unit increase in
mammographic measure and as ORs per adjusted SD
(OPERAs). To calculate OPERAs, the control popu-
lation mammographic measures are regressed on the
adjustment covariates. The standardised residuals
from this regression are an adjusted and independent
mammographic measure that effectively controls for
key population differences, strengthening our ability to
compare ORs across measurement approaches. OPERAs
are used to calculate any further metrics for assessment.

The following diagnostic statistics are considered for
the assessment:
Akaike’s information criterion (AIC): AIC is a diag-
nostic statistic derived from information theory. It is cal-
culated as minus twice the maximised log-likelihood plus
twice the number of parameters. AIC is a relative statist-
c capturing information loss, here relative to a reference
model without the mammographic measure. The smaller
the AIC, the stronger the model.

Brier score: The Brier score can be used as a calibration
measure reflecting a loss function. It is calculated as the
mean of the squared residuals. Again, the model with the
lowest Brier score is preferred.

Area under the receiver operating curve (AUC): AUC is
a measure of discrimination between cases and controls.
ROC curves visualise the trade-off between sensitivity and
specificity visualised on a plane erected by sensitivity and
1-specificity. A higher AUC means a better classification.
They are calculated using the trapezoidal rule. We will
also report a CI for the AUC bootstrapped 1000 iterations.

Partial AUC (pAUC): We will also report pAUC
focusing on the section of the Receiver Operating Char-
acteristic (ROC) curve between 0.9 and 1 (high pAUC)
and between 0 and 0.1 (low pAUC). CIs will be calculated
and reported as for the aggregate AUC.

Adjusted for covariate AUC (AAUC): The AAUC
can be adjusted for covariates. For analysing the
mammographic measure-breast cancer association, age
and BMI are critical confounders. Adjusting the AUC
takes into account that covariates may affect the control
distribution of the mammographic measure such that
the underlying probability thresholds for discriminating
between cases and controls are modelled to vary with age
and BMI.

Net Reclassification Index (NRI): The (continuous)
NRI reflects the proportion of cases correctly assigned a
higher breast cancer risk and controls correctly assigned
a lower breast cancer risk when moving from a null
model to one including a mammographic measure as
a predictor. It is calculated as the sum of NRIcases and
NRIcontrols, where NRIcases is the proportion of cases
that experience an increase in breast cancer risk minus
the proportion with a decrease, and NRIcontrols is the
proportion of controls with a decrease minus the propor-
tion with an increase in breast cancer risk.

Integrated discrimination improvement (IDI): The IDI
is calculated similarly to the NRI, with IDIcases/IDIcon-
trols representing the difference between the mean of
the predicted cancer risk from a model containing a
mammographic measure as a predictor and the mean
risk probability from the reference model without the
mammographic measure for cases/controls, respectively.
This means that the IDIcases capture the difference in
the average sensitivity of the two models and similarly,
the IDIcontrols represent the difference in the average
1-specificity.

Comparisons: We will also test for equality of AUCs,
using the AUCs. P values are reported for all possible indi-
vidual comparisons of the methods by mammogram type
as well as a joint comparison of all methods by mamma-
gram type (testing for equality of all AUCs). Hence, small
p values suggest that the challengers’ methods produce
significantly different results.

Other considerations: Large sample sizes are needed to
facilitate stratification by type of image (eg, processed vs
raw; machine manufacturer) and ethnicity. The resource
includes a mix of diagnostic and prediagnostic mamma-
grams and only the contralateral mammogram is used for
breast cancer cases.

**PATIENT AND PUBLIC INVOLVEMENT**
No patients are involved in this study. Patient data and
images provided by contributors are supplied in an anonym-
ised format, so that the data cannot be linked to personal
information. Challengers agree to treat the Challenge Data-
base and its contents as Confidential Information of the
University (or challenge contributor as the case may be);
and not attempt to identify or identify the individuals whose
information appears in the images and data.
ETHICS AND DISSEMINATION
The measurement challenge is an ongoing collaboration and we are continuing to expand the resource to include additional image sets across different populations (from contributors) and to apply additional measurement methods (by challengers). Contributors are invited to submit large sets of case–control mammographic images (raw and processed full field digital mammograms) from a range of populations, plus corresponding core data timed to the mammogram. Each contributor is responsible for the ethics approval and participant consent for their respective sample populations; written informed consent is expected unless a waiver for informed consent is obtained. Challengers are invited to apply their measurement methods to the validation set of case–controls images and provide their measures for central analysis. All contributors and challengers are required to enter a Research Collaboration Agreement with the University of Melbourne prior to participation in the measurement challenge.

The Challenge database of collated data and images will be stored in a secure data repository at the University of Melbourne.

The measurement challenge is being organised by an international committee including: JLH (University of Melbourne), JeS (University of Western Australia), JoS (UCSF), IdSS (LSHTM), MN (University of Copenhagen), VM (IARC). To collaborate or request access to data and images from the measurement challenge, contact the corresponding author at jennifer.stone@uwa.edu.au.

ADDITIONAL CONSIDERATIONS
The measurement challenge is a unique annotated resource that enables timely and prompt comparison of different mammographic measurement methods applied to full field digital mammogram images. However, full field digital mammograms differ by image type (processed vs unprocessed) and the processing differs by machine manufacturer, potentially introducing systematic bias to risk estimates. Therefore, more image sets are needed to improve statistical power and provide sufficient data to address incompatibilities between measurement methods and image type and/or manufacturer. Also, screening programmes differ by ethnicity of participants, equipment used (eg, manufacturer) and screening protocols (eg, only a small proportion store unprocessed images). Therefore, we are comparing different mammographic measures within different screening settings to inform potential users about which measurement method provides the ‘best’ predictor of breast cancer risk. Identifying women at increased risk due to high breast density could help target those who could benefit from supplemental screening using ultrasound, MRI or other modalities. Clinical trials are currently underway to determine evidence-based screening recommendations for women with dense breasts.

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Contributors JeS, JLH, JoS, IdSS, MN and VM are the Organizing Committee of the measurement challenge and made substantial contributions to the conception and design of the work. JeS, SM, NR, KR, S-HT, GU, IdSS and JLH are phase 1 contributors of images and data who made substantial contributions to the acquisition of data for the work. GL facilitates the capture, renaming, security and distribution of images in the challenge, and is involved in design and conduct of the study. DB-S and EID performed the statistical analyses and made a substantial contribution to analysis of the work. YKA, AC, JC, ZYD, CFE, RH, M-SS, DR, JeH, SM, LM, GP, NR, KR, S-HT, GU, IdSS and JLH are phase 1 contributors of images and data who made substantial contributions to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval for the Challenge is held at University of Melbourne (HREC ID 0931343.3).

Provenance and peer review Not commissioned; externally peer reviewed.

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