Supplementary information

Predicting breast cancer types on and beyond molecular level in a multi-modal fashion

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Contents

I Supplementary Methods

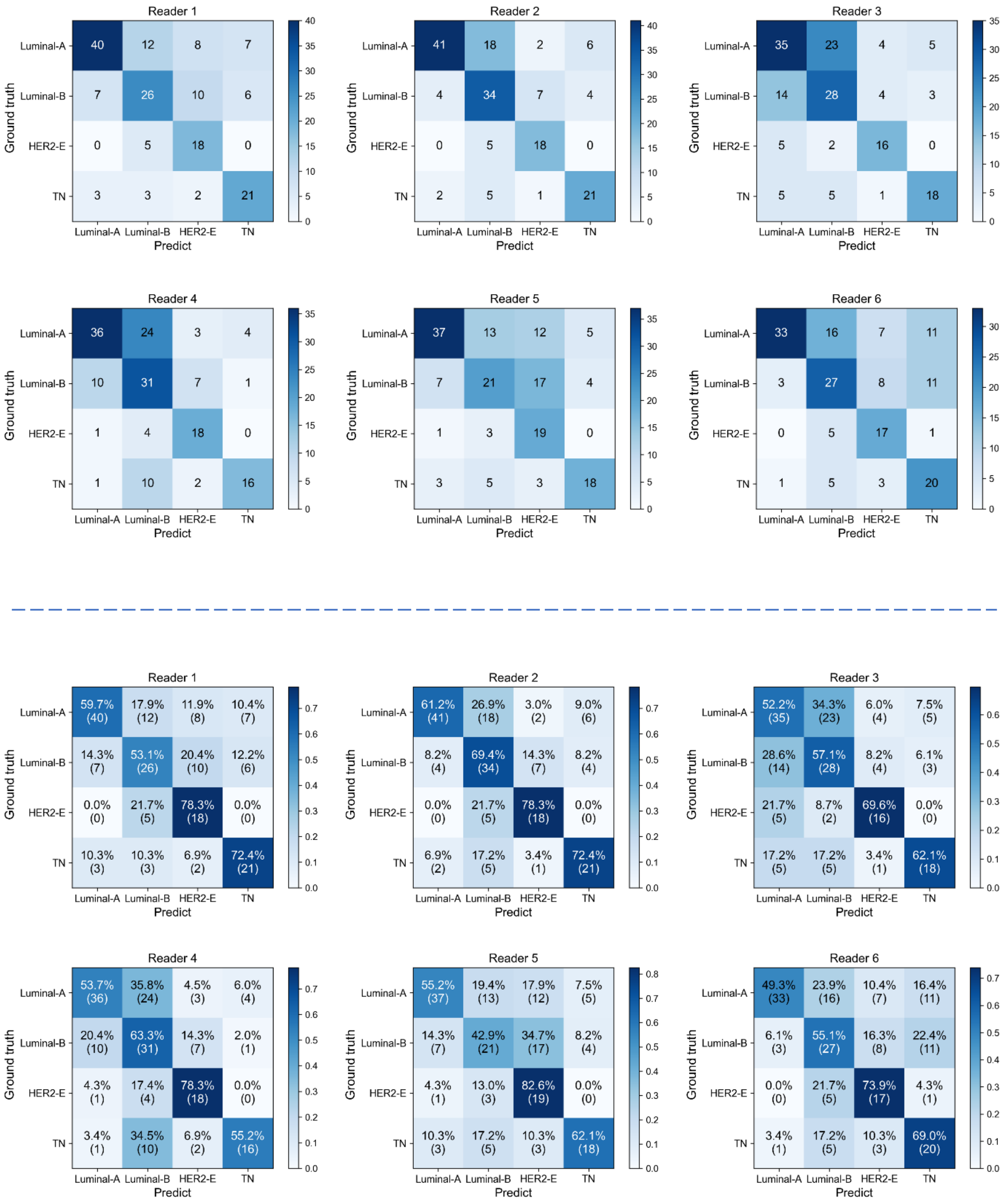
Supplementary Methods 1. Normalization

The normalization operation is a very important operation before the data is input into the deep learning model. As the raw input data values are distributed over different orders of magnitude and if normalization is not performed, some useful numerical features will be ignored, affecting the results of data analysis. Normalization is to limit the data to a certain range after certain processing. In this study, the image data of mammography and ultrasound were normalized fall into the range of 0-1 by normalization operation, and the normalization formula used was x = (x-min)/(max-min), where x represents the current pixel value, min and max represent the minimum and maximum values of pixels in the data set, respectively. It is worth noting that mammography (Equation 1) and ultrasound (Equation 2) were normalized separately since their corresponding data values are distributed on different orders of magnitude.

$$x\_mam = (x\_mam - min\_mam)/(max\_mam - min\_mam) \qquad (1)$$

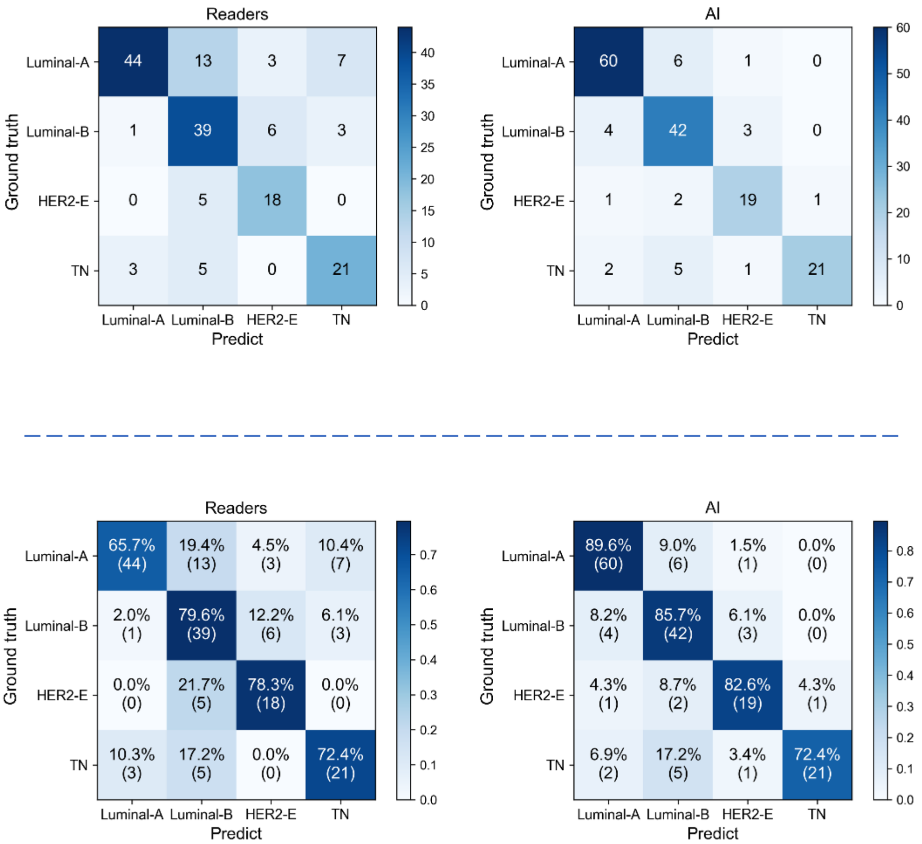
$$x\_us = (x\_us - min\_us)/(max\_us - min\_us) \qquad (2)$$

II Supplementary Figures



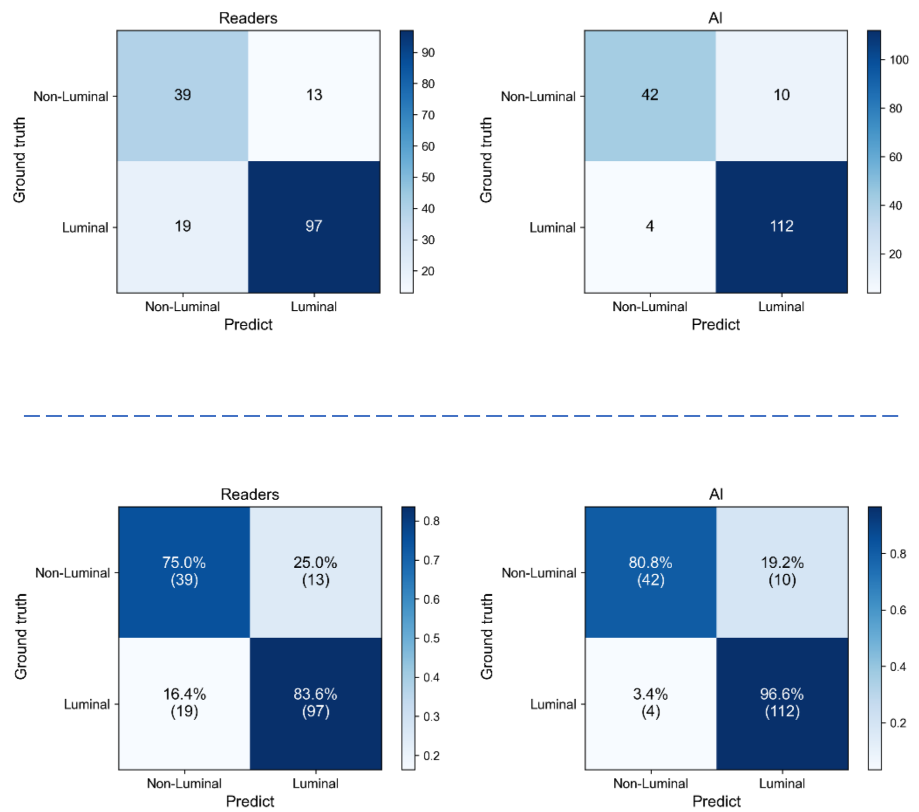
Supplementary Figure 1. Performance of six radiologists for predicting 4-category molecular subtypes of breast cancer.

Upper, original confusion matrix. Lower, normalized confusion matrix.

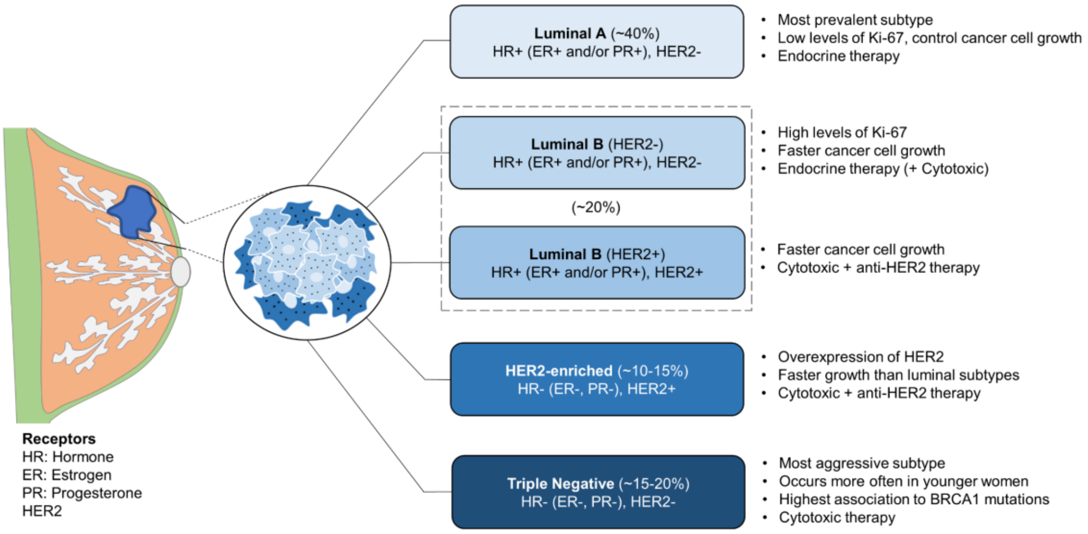


Supplementary Figure 2. Performance of radiologists (by the panel of 6 readers through majority vote) and AI for predicting 4-category molecular subtypes of breast cancer. Upper, original confusion matrix. Lower, normalized confusion matrix.

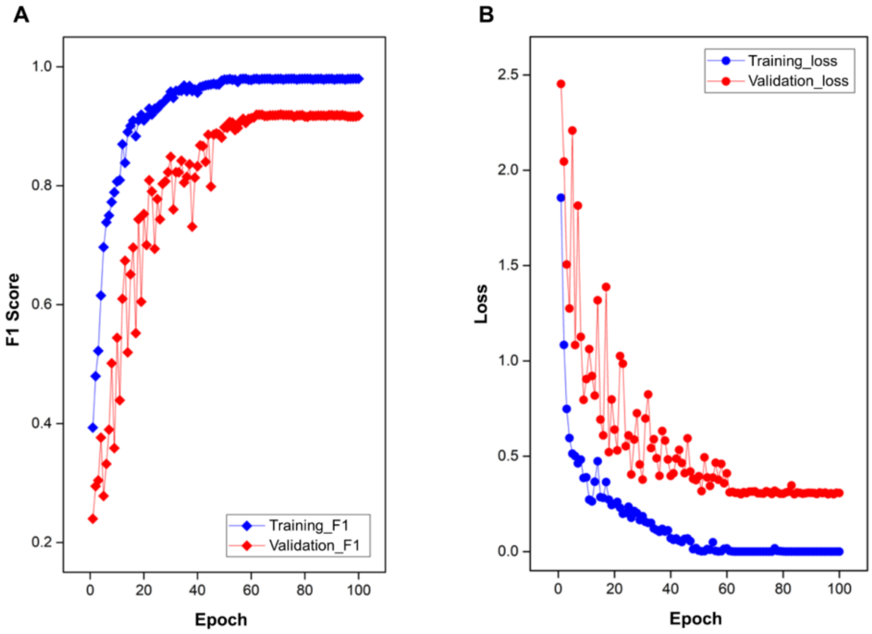
Supplementary Figure 3. Performance of six radiologists for distinguishing between Luminal disease and Non-Luminal disease. Upper, original confusion matrix. Lower, normalized confusion matrix.



Supplementary Figure 4. Performance of radiologists (by the panel of 6 readers through majority vote) and AI for distinguishing between Luminal disease and Non-Luminal disease. Upper, original confusion matrix. Lower, normalized confusion matrix.



Supplementary Figure 5. Definition and characteristics of molecular subtypes of breast cancer. HER2, human epidermal growth factor receptor 2.



Supplementary Figure 6. The F1 score and loss for training cohort (training and validation set) of the proposed model in predicting molecular subtypes of breast cancer.

III Supplementary Tables

Supplementary Table 1. Performance of radiologists and AI in for predicting 4-category molecular subtypes of breast cancer in the observer study cohort.

Reader	**Accuracy (%)**	**Precision (%)**	**Recall (%)**	**F1-score**	**MCC**
Reader 1	62.4 [55.4, 69.6]	61.4 [54.0, 68.7]	65.9 [58.3, 73.0]	0.618 [0.545, 0.696]	0.496 [0.402, 0.596]
Reader 2	68.0 [60.7, 75.0]	68.7 [61.2, 75.9]	70.5 [62.5, 77.3]	0.683 [0.607, 0.749]	0.568 [0.468, 0.659]
Reader 3	57.7 [50.0, 64.9]	60.3 [52.1, 68.0]	60.3 [52.2, 68.3]	0.597 [0.517, 0.670]	0.408 [0.296, 0.515]
Reader 4	60.1 [52.3, 67.3]	64.0 [56.2, 71.1]	62.7 [54.7, 70.2]	0.615 [0.537, 0.685]	0.455 [0.346, 0.556]
Reader 5	56.5 [48.8, 64.3]	57.8 [50.0, 65.2]	60.8 [53.3, 68.0]	0.563 [0.485, 0.639]	0.428 [0.332, 0.528]
Reader 6	57.8 [50.0, 64.9]	58.8 [51.4, 65.6]	61.9 [53.8, 69.3]	0.573 [0.493, 0.650]	0.448 [0.353, 0.541]
Panel of 6 readers	72.6 [66.1, 79.2]	72.2 [65.3, 79.0]	74.0 [66.7, 80.7]	0.719 [0.649, 0.786]	0.630 [0.540, 0.717]
Proposed (MDL-IIA)	84.4 [78.6, 89.9]	85.0 [79.1, 90.8]	82.5 [75.8, 88.6]	0.831 [0.767, 0.893]	0.780 [0.703, 0.859]

Note: Values in brackets are 95% confidence intervals [95%CI, %]. MDL-IIA, multi-modal deep learning with intra- and inter-modality attention modules. MCC, matthews correlation coefficient.

Supplementary Table 2. Performance of radiologists and AI for distinguishing between Luminal and Non-Luminal breast cancer in the observer study cohort.

Reader	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Reader 1	74.9 [67.9, 81.5]	73.1 [64.7, 81.1]	79.0 [66.7, 89.6]	88.6 [81.4, 94.7]	56.8 [45.9, 68.4]
Reader 2	81.6 [75.6, 86.9]	83.7 [76.3, 90.0]	77.0 [65.1, 88.1]	89.1 [82.9, 94.7]	67.9 [55.1, 79.1]
Reader 3	80.4 [73.8, 86.3]	86.2 [79.5, 92.4]	67.5 [53.7, 80.0]	85.6 [78.6, 91.9]	68.7 [55.8, 81.4]
Reader 4	81.7 [76.2, 86.9]	87.1 [81.0, 92.7]	69.6 [57.6, 82.0]	86.5 [80.0, 92.4]	70.7 [58.1, 82.2]
Reader 5	70.3 [63.7, 76.8]	67.2 [58.4, 75.9]	77.3 [65.3, 88.9]	86.9 [80.0, 93.5]	51.3 [40.6, 62.4]
Reader 6	71.5 [64.3, 78.6]	68.2 [59.0, 77.2]	79.0 [66.7, 89.6]	87.9 [80.7, 94.4]	52.6 [41.7, 64.3]
Panel of 6 readers	81.1 [75.0, 86.3]	83.7 [76.0, 89.8]	75.2 [62.8, 87.0]	88.3 [81.9, 94.1]	67.3 [54.5, 78.9]
Ultrasound	85.1 [79.8, 90.5]	92.1 [86.6, 96.8]	69.5 [55.5, 81.6]	87.2 [80.8, 92.7]	79.6 [67.4, 91.5]
Multi-ResNet50	88.0 [82.7, 92.9]	93.8 [88.7, 97.7]	75.1 [61.4, 87.0]	89.5 [83.9, 94.8]	84.3 [72.7, 94.1]
Multi-ResNet50+SE	89.2 [83.9, 94.0]	94.7 [90.1, 98.3]	77.0 [63.8, 88.7]	90.3 [84.6, 95.3]	86.5 [75.9, 95.7]
Proposed (MDL-IIA)	91.7 [87.5, 95.8]	96.5 [92.9, 99.2]	81.0 [69.6, 91.3]	91.9 [86.4, 96.7]	91.1 [82.2, 97.9]

Note: Values in brackets are 95% confidence intervals [95%CI, %]. MDL-IIA, multi-modal deep learning with intra- and inter-modality attention modules. SE, Squeeze-and-Excitation. PPV, positive predictive value. NPV, negative predictive value.

Supplementary Table 3. The overall architecture of the proposed model.

Modality	MG-MLO	MG-CC	US
Input 1 size	256 × 256 × 1	256 × 256 × 1	256 × 256 × 1
Stage 1	$\begin{bmatrix} 7 \times 7, 64, stride\ 2 \\ 3 \times 3\ \max pool, stride\ 2 \end{bmatrix}$ $\begin{bmatrix} 1 \times 1, 64 \\ 3 \times 3, 64 \\ 1 \times 1, 256 \end{bmatrix} \times 3$ $\begin{bmatrix} 1 \times 1, 128 \\ 3 \times 3, 128 \\ 1 \times 1, 512 \end{bmatrix} \times 4$ $\begin{bmatrix} 1 \times 1, 256 \\ 3 \times 3, 256 \\ 1 \times 1, 1024 \end{bmatrix} \times 6$	$\begin{bmatrix} 7 \times 7, 64, stride\ 2 \\ 3 \times 3\ \max pool, stride\ 2 \end{bmatrix}$ $\begin{bmatrix} 1 \times 1, 64 \\ 3 \times 3, 64 \\ 1 \times 1, 256 \end{bmatrix} \times 3$ $\begin{bmatrix} 1 \times 1, 128 \\ 3 \times 3, 128 \\ 1 \times 1, 512 \end{bmatrix} \times 4$ $\begin{bmatrix} 1 \times 1, 256 \\ 3 \times 3, 256 \\ 1 \times 1, 1024 \end{bmatrix} \times 6$	$\begin{bmatrix} 7 \times 7, 64, stride\ 2 \\ 3 \times 3\ \max pool, stride\ 2 \end{bmatrix}$ $\begin{bmatrix} 1 \times 1, 64 \\ 3 \times 3, 64 \\ 1 \times 1, 256 \end{bmatrix} \times 3$ $\begin{bmatrix} 1 \times 1, 128 \\ 3 \times 3, 128 \\ 1 \times 1, 512 \end{bmatrix} \times 4$ $\begin{bmatrix} 1 \times 1, 256 \\ 3 \times 3, 256 \\ 1 \times 1, 1024 \end{bmatrix} \times 6$
Output 1 size	16 × 16 × 1024	16 × 16 × 1024	16 × 16 × 1024
Transition	Concatenate (MG-MLO and MG-CC)		--
Input 2 size	16 × 32 × 1024		16 × 16 × 1024
Stage 2 (Intra-Modality Attention)	Intra-Self-Attention		Intra-Self-Attention
Input 3 (output 2) size	16 × 32 × 1024		16 × 16 × 1024
	16 × 16 × 1024	16 × 16 × 1024	
Stage 3	$\begin{bmatrix} 1 \times 1, 512 \\ 3 \times 3, 512 \\ 1 \times 1, 2048 \end{bmatrix} \times 3$	$\begin{bmatrix} 1 \times 1, 512 \\ 3 \times 3, 512 \\ 1 \times 1, 2048 \end{bmatrix} \times 3$	$\begin{bmatrix} 1 \times 1, 512 \\ 3 \times 3, 512 \\ 1 \times 1, 2048 \end{bmatrix} \times 3$
Output 3 size	8 × 8 × 2048	8 × 8 × 2048	8 × 8 × 2048
Transition	Concatenate (MG-MLO, MG-CC and US) (8 × 24 × 2048)		
Stage 4 (Inter-Modality Attention)	Inter-Self-Attention		
	Reshape (8 × 8 × 6144)		
	Inter-Channel-Spatial-Attention		
Output 4 size	(8 × 8 × 2048) × 3		
GAP layer	GAP layer		
Output 5 size	(1 × 1 × 2048) × 3		
FC layer	FC layer		
Output	Luminal A, Luminal B, HER2-enriched and Triple-negative		

Note: MG, mammography. US, ultrasound. MLO, medio-lateral oblique. CC, cranio-caudal. GAP, Global Average Pooling. FC, Fully-connection.

Supplementary Table 4. Experience levels of the six radiologists involved in our reader study.

Reader	Years of experience
Reader 1	6
Reader 2	14
Reader 3	16
Reader 4	9
Reader 5	13
Reader 6	20
Average	13

Note: Years quoted are years practicing as dedicated breast radiologist. This means after medical school, general radiology training and either a fellowship or a PhD in breast imaging.