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Quantra™ 2.2 Software
Design Intent and Clinical Performance

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Introduction

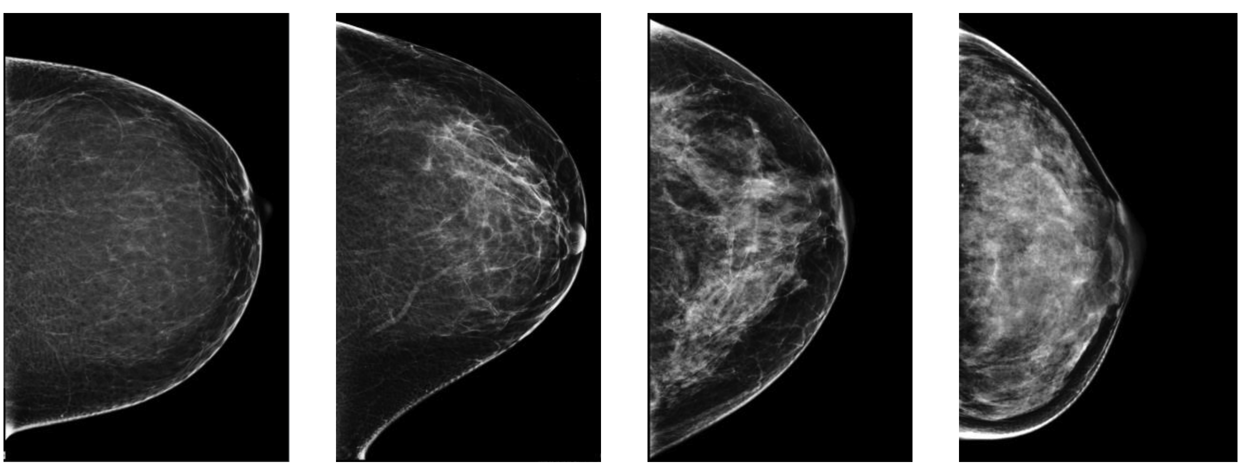
This white paper is intended to introduce the latest version of Hologic's breast density product, Quantra 2.2 software. It will discuss why automated breast density categorization could be advantageous, review changes in guidance language provided by the American College of Radiation (ACR) BI-RADS Atlas revision for breast composition categorization and go over the rationale behind the design of Quantra 2.2 software algorithm in comparison with currently produced version of Quantra software. The results of the study to assess clinical performance of Quantra 2.2 software for its FDA approval will also be presented.

BI-RADS breast composition categories

American College of Radiology (ACR) publishes a BI-RADS Atlas to facilitate standardized reporting of mammographic interpretation by interpreting physicians. Assessment of breast composition categories through visual inspection of images is a vital component of mammographic reporting and conveys information about mammographic sensitivity to detect lesions and the relative risk for breast cancer. Figure 1 shows example mammograms representing these four categories.

Why fully automated density category assessment is advantageous

It has been well-documented that there is a large amount of intra[1] and inter[2,3] reader variability in visual assessment of breast density categories. It has also been shown that the level of experience and training affects the BI-RADS reporting[4]. In addition, a possibility of an unintended bias that is driven by supplemental screening decisions that may be based on reported the density category cannot be denied. Also, legislation in several states that requires patients to be informed of breast density and the potential for decreased mammographic sensitivity and increased cancer risk also may play a role in an inadvertent bias in the reporting of density category. Therefore, fully automated methodology can offer a completely unbiased and reproducible option to assess and report breast density category. Hologic Quantra software offers this fully automated choice, which is well-integrated in existing mammographic workflow.



a — Fatty b — Scattered Fibroglandular c — Heterogeneously dense d — Extremely dense

Figure 1. Breast composition categories described in ACR BI-RADS Atlas

Modification in ACR guidelines for BI-RADS density categorization

ACR published a modification in guidelines for breast composition category reporting as a part of the 5th Edition of BI-RADS Atlas[5]. In spite of this change, the overall goal of reporting the categorization has remained the same, namely, to visually estimate the content of fibroglandular density tissue within the breasts and segregate them into four categories. In the 4th Edition of BI-RADS, each category was associated with a quartile range of percentage (%) of dense tissue. In the 5th Edition of BI-RADS Atlas this range of percentage is no longer included. Figure 2 shows the change between Edition 4 and Edition 5 as proposed by ACR.

BI-RADS Category	Description
a	The breast is almost entirely fat.
b	There are scattered fibroglandular densities.
c	The breast tissue is heterogenously dense, which could obscure detection of small masses.
d	The breast tissue is extremely dense. This may lower the sensitivity of mammography.

Figure 2. Modification of breast composition categories description in BI-RADS Atlas from Edition 4 to Edition 5. BI-RADS 5th Edition no longer includes ranges of percentage of dense tissue

This modification was done to emphasize the text description of breast density, which reflects the masking effects of dense tissue on mammographic appearance of soft tissue lesions. According to the committee on BI-RADS, association of subjectively estimated breast density with changes in sensitivity due to obscuration of lesions is clinically more important than relatively smaller effect of percentage of breast density. The committee further indicated that until the time published literature provides sufficient evidence that volume-based breast density data and corresponding validated percentage cut points can be reproducibly estimated, the committee would not include percentage ranges of glandular density for BI-RADS density categorization.

Importance of dense tissue pattern and its masking effect

There is sufficient evidence that mammographic sensitivity, as well as inherent risk of occurrence of breast cancer, is related to breast density[6-7]. However, the dependence of risk, as well as masking on density is much more complex than simply the amount of fibroglandular tissue. A few tightly overlapping areas of dense tissue can cause more obscuration compared to evenly distributed dense tissue in a breast with the same amount of percentage dense tissue. Figure 3 illustrates this concept with graphics similar to the"Where's Waldo" exercise, where the goal is to find

a. It is easier to spot the character with a patterned shirt amongst the crowd that is distributed over a larger space.

Figure 3 "Where is Waldo"-like illustration to demonstrate that effect of distribution and pattern of objects play a more crucial role than density itself in the task of detecting an object.

character wearing the patterned shirt in a crowded scene. It is harder to spot the character with a patterned shirt in picture (b), where the crowd is concentrated in one part of the graphic, compared to picture (a), where the crowd is more distributed over a larger space, even though there are the same number of characters in both graphics.

There is a growing body of evidence that pattern and texture of fibro glandular tissue plays an equally important role in mammographic cancer risk prediction[8-10]. This fact is reflected in the modifications proposed in ACR BI-RADS Atlas. Figure 4 shows a schematic illustrating how breast composition categorization may be affected under new BI-RADS guidelines.

Figure 4 is an illustration showing two breasts with quantitative glandular density in the second quartile range (25% to 50%) as per description in BI-RADS Atlas 4th Edition. Therefore, both these images may have been categorized as “b” per this guidance. However, the distribution of density in the image on the top is uniform and therefore, has a lower chance of masking a small lesion. On the other hand the glandular tissue in the concentrated upper outer quadrant of the right breast is sufficiently dense for a possibility of obscuring a small lesion and therefore, according to BI-RADS Atlas Edition 5 may be categorized as “c”.

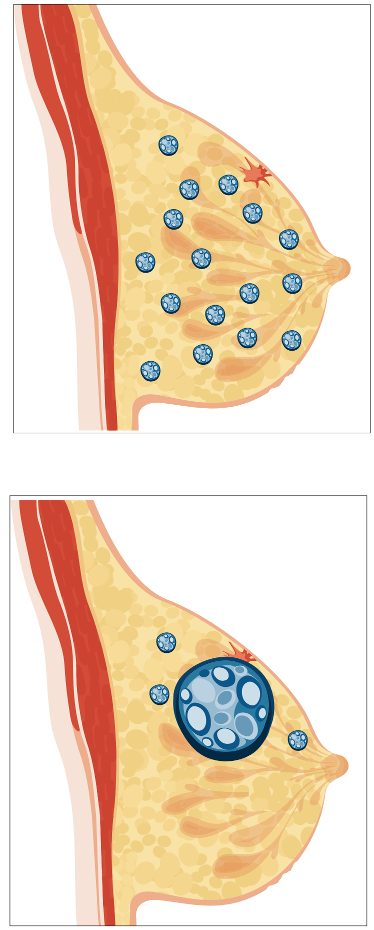


Figure 4. Illustration showing two breasts with quantitative glandular density in the second quartile range (25% to 50%) as per description in BI-RADS Atlas 4th Edition.

b. It is more difficult to spot character with a patterned shirt when the same crowd is concentrated in a limited space.

Design intent of Quantra 2.2 software

Previously marketed version of Quantra software was designed based on BI-RADS Atlas 4th edition which takes into account percentage of dense tissue. This method first estimated the percentage (%) of volumetric breast density using an X-ray attenuation model for fat and dense tissue using mammographic acquisition parameters. Then, the breasts were segregated into four categories purely using validated threshold values of estimated volumetric density. The software also displayed these thresholds, the corresponding volumetric density values, as well as corresponding area density and other associated parameters calculated based on volumetric dense tissue measurement. While this method provides quantitative estimates of the amount of dense tissue relative to breast volume, such method clearly does not specifically take into account masking effect resulting from local concentrated densities that are governed by the pattern of parenchymal tissue distribution.

Hologic has been continuously striving to improve Quantra software. Through analysis of feedback received from our customer base that has been using the initial versions of this product, Hologic has incorporated enhancements to the image processing algorithms that estimate breast tissue composition characteristics. In response to modifications to the description of breast composition categories in the 5th Edition of B-IRADS Altlas, Hologic invested in methodologies that focused on understanding breast tissue distribution pattern and texture, rather than volumetric breast density alone. Breast composition categories assigned by Quantra 2.2 will incorporate the masking effect of fibro-glandular tissue distribution in compliance with the latest guidance from ACR. As a result, the volumetric density and associated parameters that were part of the currently marketed Quantra product will no longer be displayed in the output of Quantra 2.2 software. Elimination of the breast density related numerical parameters from display of Quantra 2.2 software was a mandatory requirement posed by the FDA for a product that is compliant with BI-RADS Edition 5.

Quantra 2.2 software: Analysis based on machine learning

Machine-learning-based algorithms are known to perform well for a classification problem that involves identifying category of a new observation, on the basis of knowledge based on a training set of data containing observations whose categories are known. Breast density categorization using parenchymal pattern and texture is such a classification problem. As a part of continuous improvement efforts of various products, Hologic routinely collects images from mammographic studies along with corresponding radiology reports. Therefore, a training set of thousands of mammographic images with corresponding radiologist-assigned BI-RADS density categories was readily available for training a machine- learning-based algorithm to automatically categorize breasts into BI-RADS-like categories. Quantra 2.2 software is a result of efforts of using Hologic's vast database of images with known breast density BI-RADS categories to achieve a fully automated breast density categorization leveraging modern artificial intelligence and machine learning techniques.

Quantra 2.2 software will be the latest release in a series of enhancements to Hologic's automated breast density measurement offering. The latest algorithm uses a Multi-Class Support Vector Machine (SVM)[11] based classification technique to segregate breast types into four categories based on breast parenchymal tissue pattern and texture representation. A four class SVM model was trained using over 6,000 mammographic studies for which the BI-RADS category assigned by radiologists at the time of screening were available as ground truth. The training incorporated focus on proprietary statistical features that represent the distribution and pattern of pixel values inside the breast, rather than absolute gray values alone. A model trained with such pattern and texture-based features is intended to segregate the breast composition categories based on tissue distribution and masking effect ,rather than volumetric measurement alone. With this technology, the Quantra 2.2 software algorithm automatically estimates a breast composition category in alignment with the new guidelines provided in BI-RADS Atlas Edition 5.

Clinical evaluation of Quantra 2.2 software

As a part of supporting evidence for U.S. approval of Quantra 2.2 software under FDA guidelines, Hologic conducted a study using images from 230 screening examinations with 4 standard mammographic views. All these images were acquired using the Hologic Selenia® Dimensions® product in "combo" mode; meaning tomosynthesis and conventional 2D images were acquired from the same subject under the same compression.

Ground truth estimation

Five readers independently assigned the BI-RADS breast density categories by reviewing this set of 230 cases. For each examination, tomosynthesis images as well as conventional 2D images were available for review. The readers were instructed to follow the guidelines in 5th Edition of BI-RADS Atlas issued by ACR. The ground truth breast density category for each examination was obtained by calculating the median value of the category scores assigned by the 5 readers.

Quantra density category evaluation

Similar to the previous version, Quantra 2.2 software will also have a user selectable option to analyze either conventional 2D or tomosynthesis images in the instances where both images are available for analysis when combo mode is used. For those customers using only one of those images (either only conventional 2D or only tomosynthesis HD) Quantra software will, of course, analyze the available mode of images for estimation of breast density results. Therefore, both conventional 2D as well as tomosynthesis images were analyzed and compared independently against the ground truth BI-RADS categories obtained by analyzing the assignments by 5 readers. While analyzing tomosynthesis images, Quantra software uses the center projection image from the tomosynthesis acquisition.

Results

Study population distribution

As described previously, ground truth for each case was derived from the median value of the categories assigned by each of the 5 readers. The following table shows the distribution of the cases after assessment of categories by human readers using ACR BI-RADS 5th Edition.

Consensus Density Category (BI-RADS 5th Edition)	Cases per Category
a	32
b	81
c	85
d	32
Total	**230**

Assessment of results and contingency tables

Assessment of agreement between two independent methods for estimation of categorical measurements, such as BI-RADS density categories, is typically done using contingency tables. A contingency table is a two-way matrix that tallies observations of categories as measured by two independent methods. If the two methods are in complete agreement on all instances, then all the frequency counts fall on the diagonal of contingency table and all non-diagonal positions contain zeros. However, typically there is only moderate agreement between various readers in assessment of breast density[2] and the frequencies at non-diagonal positions in the cells are larger than zero.

Inter-reader variability

As previously described, 230 mammographic studies were assessed by 5 radiologists independently for BI-RADS density category assessment for estimation of ground truth. This data presents an opportunity to understand reader variability using 10 pairs of observations by two independent readers on each of the 230 cases. This data showed that the percentage number of cases on which the two radiologists agreed for the BI-RADS category assessment ranged from 63% to 86% with an average of 76%. These percentage agreement quantities from our internal study are similar to those reported in literature for inter-reader agreement. Table 1 shows a cumulative contingency table of categories assigned by each pair of the radiologists who participated in the ground truth estimation process. This result shows that there was an agreement on only 76% of observations between the two readers. This result is important to keep in mind while reviewing outcomes from comparison of Quantra software estimated breast density categories and reader-assigned ground truth categories.

	Reader A				
		a	b	c	d
Reader B	a	246	78	0	0
	b	94	673	84	0
	c	0	62	649	165
	d	0	0	63	186
			Observations with Agreement		1754
			Total #		2300
			Overall Agreement (%)		76%

Table 1. Cumulative contingency table of BI-RADS categories assigned by pairs of independent radiologists participating in ground truth estimation.

Assessment of Quantra against radiologists' ground truth

Assessment of agreement between Quantra software density categories and radiologist-assessed ground truth categories using BI-RADS Edition 5 can be similarly represented in form of a contingency table, which is a two-way matrix that tallies observations of categories assigned by Quantra software against the estimated ground truth category (previously described) for each mammographic study.

Table 2 shows the contingency table of categories assigned by Quantra 2.2 software using conventional 2D images against the ground truth using BI-RADS 5th Edition.

	Quantra 2.2 software Conventional 2D Images				
		a	b	c	d
"Ground Truth" BIRADS-Ed5	a	21	11	0	0
	b	9	64	8	0
	c	0	1	61	23
	d	0	0	1	31
			Cases with Agreement		177
			Total #		230
			Overall Agreement (%)		77%

Table 2. Comparison of Quantra 2.2 categories using conventional 2D images against ground truth BI-RADS Edition 5 categories by radiologists.

Table 3 shows the frequency distribution for categories assigned by Quantra 2.2 software using tomosynthesis center projection images against the ground truth using BI-RADS 5th Edition.

	Quantra 2.2 software Tomosynthesis Images				
		a	b	c	d
"Ground Truth" BI-RADS Ed5	a	20	12	0	0
	b	11	61	9	0
	c	0	7	53	25
	d	0	0	1	31
			Cases with Agreement		165
			Total #		230
			Overall Agreement (%)		72%

Table 3. Comparison of Quantra 2.2 categories using tomosynthesis images against ground truth BI-RADS Edition 5 categories by radiologists.

Based on results summarized in Table 1 and Table 2, the overall percentage agreement between Quantra 2.2 software and radiologists' established ground truth is in the range of typical inter-reader variability. Although overall agreement percentage for tomosynthesis images is lower than conventional 2D images, this variation is purely due to differences in the source data, rather than any systematic disadvantage of tomosynthesis images for Quantra software. Considering the large inter-reader agreement range of 63% to 86%, agreement results from this study using both conventional 2D images, as well as tomosynthesis images, support clinical efficacy of Quantra in estimating breast density category.

In addition, grouping categories a+b as "fatty" and c+d as "dense" can be significant with respect to triage management in a screening environment. Therefore, analysis was also done to obtain following additional contingency tables using the same data, but with only two, "fatty" and "dense," categories.

Table 4 shows Quantra 2.2 software using conventional 2D images against the ground truth using "fatty" vs. "dense" assessment.

	Quantra 2.2 software conventional 2D images		
"Ground Truth" BI-RADS Ed5		**Fatty**	**Dense**
	Fatty	105	8
	Dense	1	116
	Cases with Agreement		221
	Total #		230
	Overall Agreement (%)		96%

Table 4. Comparison of Quantra 2.2 categories using conventional 2D images against ground truth "fatty vs. dense" categories by radiologists.

Table 5 shows Quantra 2.2 software using tomosynthesis images against the ground truth category using "fatty" vs. "dense" assessment.

The overall agreement of the Quantra software-based triaging method between fatty vs. dense breasts was observed to be well above 90% when compared with radiologists' ground truth.

	Quantra 2.2 software tomosynthesis images		
"Ground Truth" BI-RADS Ed5		**Fatty**	**Dense**
	Fatty	104	9
	Dense	7	110
	Cases with Agreement		214
	Total #		230
	Overall Agreement (%)		93%

Table 5. Comparison of Quantra 2.2 categories using tomosynthesis images against ground truth "fatty vs. dense" categories by radiologists.

Conclusion

Hologic has been investing in continuous improvement of Quantra software to offer a fully automated breast composition categorization that is well-integrated into clinical workflow. Quantra 2.2 software is in alignment with the modifications proposed by ACR BI-RADS committee. Quantra 2.2 methodology uses the most advanced machine-learning-based algorithms that are trained using thousands of mammographic studies. Quantra software demonstrated a high percentage overall agreement with reader assessment-based ground truth in Hologic's internal study. Quantra's overall agreement with ground truth was similar to inter-reader agreement, indicating that Quantra can be used in clinical practice for fully automated breast composition categorization. In addition, the study also showed that for triaging the patients into "fatty vs. dense," Quantra can achieve more than 90% agreement with radiologists' assessment.

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