BIOSTATISTICS CONSULTING, LLC

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CONFIDENTIAL

Statistical Analysis Plan

for

FUJIFILM Medical Systems U.S.A., Inc.

protocol

FMSU2017-002A: A Multi-Reader Multi-Case Controlled Clinical Trial to Evaluate the Comparative Accuracy of the Fujifilm DBT plus S-View versus FFDM Alone in the Detection of Breast Cancer – A Pilot Study

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ABBREVIATIONS

AUC	area under the receiver operating characteristic (ROC) curve
BCL	Biostatistics Consulting, LLC
BI-RADS	Breast Imaging Reporting and Data System *BI-RADS® is a registered trademark of the American College of Radiology*
CC	craniocaudal
CRF	case report form
DBT	digital breast tomosynthesis
eCRF	electronic case report form
FFDM	full field digital mammography
Fujifilm	FUJIFILM Medical Systems U.S.A., Inc.
MLO	mediolateral oblique
MRMC	multi-reader multi-case
POM	probability of malignancy
ROC	receiver operating characteristic
S-View	synthesized view (2D)

1. Introduction

This document provides the statistical analysis plan (SAP) for FUJIFILM Medical Systems U.S.A., Inc. (Fujifilm) pilot study protocol FMSU2017-002A, which is a retrospective, multi-reader, multi-case (MRMC) pilot study to be conducted with an enriched sample of approximately 100 cases and six (6) board-certified radiologists with a range of experience who will be trained to read and evaluate Fujifilm digital breast tomosynthesis (DBT) and synthesized view (S-View) 2D images. Each radiologist will review full field digital mammography (FFDM) and DBT plus S-View images for each case in a counterbalanced design with an approximately four (4) week memory washout period. The purpose of the pilot reader study is to provide credible performance estimate information in order to properly plan, design, and power the pivotal study. The results of this pilot study may be used to provide supplemental data for an FDA submission; they are not intended to serve as a basis for FDA approval.

This SAP is based on protocol FMSU2017-002A Final Version 1.0 dated 12 October 2017. If the protocol is amended in a manner that requires this SAP to be revised, Fujifilm and Biostatistics Consulting, LLC (BCL) will finalize the revised SAP before locking the database for the primary analysis. If there is a conflict between the protocol and this SAP, the language in this SAP as approved by BCL, Fujifilm, and the study Principal Investigator shall prevail.

1.1. Study Endpoints

The primary endpoint is non-inferior per-subject average area under the receiver operating characteristic (ROC) curve (AUC) requiring correct lesion localization for DBT plus S-View versus FFDM. The secondary endpoints, all as per-subject average for DBT plus S-View versus FFDM, are superior AUC, non-inferior and/or superior recall rate for all non-cancer cases, superior specificity, non-inferior and/or superior sensitivity, and non-inferior recall rate for all cancer cases.

2. Study Design

Protocol FMSU2017-002A is a retrospective, MRMC study of Fujifilm DBT plus S-View to be conducted with an enriched sample of 100 cases obtained from multiple image acquisition centers on Fujifilm protocol FMSU2013-004A “Acquisition of Digital Mammography and Breast Tomosynthesis Images for Clinical Evaluation of Fujifilm Digital Breast Tomosynthesis,” and six (6) radiologist readers with varying experience levels some of whom have limited

experience reading 2D synthetic images. The study employs a fully factorial, counterbalanced crossover design in which all readers review images from all cases in two (2) visits separated by a memory washout period of approximately four (4) weeks. Each reader will read half the cases as FFDM and the other half as DBT plus S-View during Visit 1, and the complementary FFDM and DBT plus S-View images during Visit 2.

2.1. Study Population (Cases)

Protocol FMSU2017-002A will include an enriched sample of 100 cases obtained from multiple image acquisition centers on protocol FMSU2013-004A. All cases for this pilot MRMC reader study will meet the following eligibility inclusion and exclusion criteria:

Inclusion Criteria

- Eligible subjects under protocol FMSU2013-004A, defined as female subjects with known true clinical status and with complete FFDM and DBT examinations, in which there is sufficient anatomical coverage, sufficient contrast, and no significant motion or other artifacts, as determined by the image-acquisition sites.
- Meet none of the exclusion criteria under protocol FMSU2013-004A.

Exclusion Criteria

- Subjects who are in violation of protocol FMSU2013-004A.
- Subjects who meet exclusion criteria under Fujifilm protocol FMSU2013-004A.
- Subjects with unknown clinical status.
- Any subject whose positive mammogram was not read during the truthing process will not be considered for the pilot reader study.

Case selection. Cases selected for this study were, to the extent possible, those that BCL selected per approved case selection specifications for Fujifilm protocols FMSU2013-004E "A Multi-Reader Multi-Case Controlled Clinical Trial to Evaluate the Comparative Accuracy of the Fujifilm FFDM Plus DBT Versus FFDM Alone in the Detection of Breast Cancer – A Pilot Study" and FMSU2013-004F "A Multi-Reader Multi-Case Controlled Clinical Trial to Assess the Adequacy of Fujifilm FFDM and DBT Reader Training Program – A Pilot Study." Starting with this case list, Fujifilm replaced cases that were lost to follow-up or otherwise not available to arrive at a final case list for this pilot study FMSU2017-002A.

Demographic and clinical characteristics. Demographic and clinical characteristics were obtained on Fujifilm protocol FMSU2013-004A (see **Appendix 1** for relevant form pages). The sample includes 18 cancer cases and 82 non-cancer cases comprised of 17 benign cases, 19 recall cases, and 46 normal cases. Cases without biopsy are from the screening pathway and have one-year negative imaging follow-up.

2.2. Study Radiologists (Readers)

Approximately six (6) radiologists will participate as study readers. Readers may be radiologists of varying experience levels, from both community and academic practices, some of whom have limited experience reading 2D synthetic images. Reader information is recorded on a dedicated questionnaire (**Appendix 1**).

Qualifications. All readers must be board-certified and Mammography Quality Standards Act (MQSA)-qualified for both FFDM and DBT interpretation.

Training. Readers will receive approximately two hours of training in the evaluation of DBT plus S-View images. Training will also consist of a hands-on session at the workstation to provide the readers with an overview of its DBT-specific functionality. For each view, mediolateral oblique (MLO) and craniocaudal (CC) 2D FFDM and the complementary S-View image for the same view will be shown with the DBT images. The training will also emphasize that the S-View images alone will not be used for diagnosis, and scoring will be based on the appearance of the lesion on the DBT images.

3. Test Methods

3.1. Reference Standard

The reference standard for cancer and benign cases is biopsy proof. The reference standard for recall and normal cases is one-year follow-up imaging (320 to 455 days inclusive). The truthers' lesion type(s) and location(s) for all cancer cases in both modalities (FFDM and DBT plus S-View) will be recorded on an electronic case report form (eCRF; **Appendix 1**).

3.2. Randomization

Randomization was performed by BCL per the approved "Randomization Specifications for FUJIFILM Medical Systems U.S.A., Inc. protocol FMSU2017-002A: A Multi-Reader Multi-Case Controlled Clinical Trial to Evaluate the Comparative Accuracy of the Fujifilm DBT plus

S-View versus FFDM Alone in the Detection of Breast Cancer – A Pilot Study," dated 28 September 2017. The randomization created for protocols FMSU2013-004E and -004F was updated for the replacement cases, and for a change in workstation capabilities that will allow use of a worklist rather than requiring cases to be loaded on each reader's workstation in her or his assigned interpretation order.

BCL assigned the case interpretation order for protocols FMSU2013-004E and -004F according to randomization specifications approved 1 April 2015. The 100 cases were randomly allocated into two (2) sets of 50 cases each, case subsets A and B. Allocation was balanced to the extent possible in the case sample with respect to 1) reference standard status (cancer, benign, recall, normal), 2) breast composition (fatty or dense), 3) presence of calcifications, and 4) image acquisition site. For the current study BCL retained the protocols FMSU2013-004E and -004F randomization lists for Visit 1 and Visit 2 for readers R01, R02, R03, R04, R06, and R07. The randomization list for reader R07 was used in place of the list for reader R05 to ensure counterbalancing within this single pilot study, in contrast to overall counterbalancing in the earlier pair of pilot studies. Reading order was randomly determined for each reader.

3.3. Image Review Procedures

Study readings will occur at International HealthCare, LLC (Norwalk, CT) between 4 November 2017 and 9 December 2017. Each reader will read both FFDM and DBT plus S-View images for each case, separated by a memory washout period, on the ASPIRE Bellus II workstation.

3.4. Image Interpretation Results

Readers will be prompted by scribes, who will enter each reader's responses in the reader eCRF (**Appendix 1**). For each case on each read, the reader will first note whether there are mammographic findings. If the answer to this question is "no" the reader will be asked to provide a BI-RADS assessment category of 1 or 2, a probability of malignancy (POM) score in 0% through 100%, and a recall decision of "no." If the reader answers "yes" to whether there are mammographic findings the reader will be asked to confirm an initial BI-RADS assessment category of 0, and will then provide detailed information for up to three (3) suspicious findings (reader lesions):

- Location (including breast [right or left], diagram location [1 – 9 or combinations when the finding is in multiple diagram sections] within view [right CC, left CC, right MLO, left MLO], and coordinates for each of CC and MLO [N/A if not seen on that view; or X, Y, and for DBT only, Slice])
- Type, as mass, asymmetry, calcification, architectural distortion, or other with description. The reader may check all that apply.
- Forced BI-RADS assessment category 1, 2, 3, 4, or 5
- POM in 0% through 100%

The reader will then be asked for her or his overall recall decision (yes or no), forced BI-RADS assessment category, and POM score, for the case.

In cases with mammographic findings, consistency of BI-RADS scores, POM scores, and recall decisions will not be forced – for example, readers will be permitted to use the full range of POM scores for a finding no matter what BI-RADS score they assign to it.

3.5. Lesion Matching (Scoring)

An expert not associated with diagnosing cases at the image acquisition sites or serving as a study reader will perform lesion matching to determine whether the location and type of any reader findings match a lesion annotated by the truther. Lesion matching will be performed for all malignant lesions in cancer cases. The lesion matcher's results will be recorded on an eCRF (**Appendix 1**).

3.6. Blinding / Masking

The readers will be told that the samples of cases do not represent a standard screening population, and will be blinded to the actual distribution and nature of the set of images they will be asked to review. Readers will be masked to the reference standard and image acquisition interpretations (under Fujifilm protocol FMSU2013-004A) for each case. Readers will not have access to prior mammograms or other clinical information. All readers will perform their interpretations independently.

4. Statistical Methods

Informed consent. By approving this SAP, Fujifilm confirms the following: All subjects whose images were acquired under FMSU2013-004A and selected for this study were consented.

As part of the consent process, subjects agreed that image data and supporting documentation could be used for future research and investigations. Each reader will be consented before initiating the reader study.

Masking to protect identities. Study case identification numbers and study reader numbers will be assigned to all cases and readers, and used to protect their identities in statistical analysis and in reporting of results.

Statistician not blinded. Because the reader data on lesion locations only includes Slice for DBT, the statistician will not be blinded to reading condition.

General conventions: Descriptive summaries. Baseline descriptive summaries will include the distribution of demographic characteristics and clinical characteristics, including characteristics specific to malignant and, if appropriate, benign lesions. We also will provide summaries across readers of the per-subject number of findings, BI-RADS scores, POM scores, and per-subject recall scores, for the FFDM and DBT plus S-View readings. These may be cross-classified by, for example, presence of malignant lesions. Categorical variables (such as cancer type and breast tissue composition) generally will be summarized using frequencies and proportions or percentages, while continuous variables generally will be summarized using means and standard deviations (SDs), and/or medians and quartiles or ranges. Missing values generally will be reported as such in these descriptive summaries.

General conventions: Statistical inferences. Uncertainty in estimates of diagnostic accuracy will be quantified through confidence intervals (CIs). Unless otherwise noted, statistical inference procedures (hypothesis tests, CIs) are two-sided with significance level alpha = 0.05 and corresponding confidence level 0.95. Statistical inferences for proportions (for example, sensitivity and specificity) may use the binomial distribution or other exact methods rather than normal approximations, for example, when sample sizes are small and/or when proportions are close to zero or one. Results will be presented by reader using reader numbers to mask reader identities, and averaged across readers.

4.1. Study Samples (Analysis Sets)

We plan to include all readers' interpretations of all cases in the analysis set. If any protocol deviations or violations occur the statistician will evaluate these to determine their impact on the

validity of the study data; and will determine whether any affected data points should be excluded from analysis.

Unit of analysis. The unit of analysis on this study is the subject (case).

4.2. Treatment Assignment

This is a retrospective study for which imaging and clinical management occurred prior to case selection. All cases will be evaluated the same way by all study readers, such that there are no treatment assignments or treatment groups.

4.3. Multiple Centers (Pooling)

Fujifilm obtained images from multiple centers. The protocol for data submission, quality review passed by all images, and reference standard status determination for all images used in the pilot MRMC study were common. Cases will be pooled across enrolling centers for interpretation on the pilot MRMC study using common interpretation protocol and eCRFs, and results of interpretation sessions will be monitored. The scoring of (lesion matching for) reader interpretations will follow a common process. Results for any particular reader therefore will be pooled across enrolling centers.

4.4. Derived Variables

Per-subject BI-RADS, POM, and recall scores requiring correct lesion localization will be derived as shown below. The general principle is that even at the subject level, credit is only given for identifying a subject with cancer if the reader marks findings in at least one location with cancer. Findings that do not match the location of a malignant lesion are ignored for cancer cases in the per-subject analyses but may be reported, generally in an appendix.

When computing sensitivity and specificity based on BI-RADS, a score of 4 or 5 constitutes a positive test result. A cutoff score of BI-RADS 3 or higher may also be used to compute the sensitivity and specificity in secondary analyses.

Per-Subject Scoring: POM and BI-RADS. The primary endpoint is per-subject AUC based on POM scores requiring correct lesion localization. Secondary endpoints include per-subject sensitivity requiring correct lesion localization and specificity based on BI-RADS categories. Scores for use in these analyses will be derived by the statistician as summarized in **Table 1** on page 13.

Per-Subject Scoring: Recall. Secondary endpoints include per-subject recall rate for non-cancer cases and separately for cancer cases requiring correct lesion localization, based on a separate yes/no question. Scores for use in this per-subject analysis will be derived by the statistician as summarized in **Table 2**.

True Positive, False Negative, True Negative, and False Positive. In per-subject analysis of sensitivity and specificity:

- A true positive (TP) occurs when a case contains one or more cancerous lesions and the per-subject BI-RADS score requiring correct lesion localization is 4 or 5.
- A false negative (FN) occurs when a case contains one or more cancerous lesions and the per-subject BI-RADS score requiring correct lesion localization is 1, 2, or 3.
- A true negative (TN) occurs when a case does not have any cancerous lesions and the per-subject BI-RADS score is 1, 2, or 3.
- A false positive (FP) occurs when a case does not have any cancerous lesions and the per-subject BI-RADS score is 4 or 5.

When computing recall rates requiring correct lesion localization, a recall occurs when a case has per-subject recall score equal to yes.

4.5. Subgroups

Analyses of per-subject recall rate for non-cancer cases and specificity are limited to the subgroup of cases without cancer. Analyses of per-subject sensitivity and per-subject recall rate for cancer cases are limited to the subgroup of subjects with cancer. We may also 1) analyze AUC, sensitivity, specificity, and/or recall rate in the subgroup of women with dense breasts; and/or 2) perform per-lesion analysis of sensitivity in subgroups defined by lesion type (masses with or without calcifications, focal asymmetries, and/or architectural distortions in one subgroup, and calcifications in another subgroup).

Table 1. Per-Subject POM and BI-RADS Scores Requiring Correct Lesion Localization

Reference standard	Reader's interpretation	Per-Subject POM and BI-RADS
No malignancies in this case	No findings in this case	**POM:** Same as POM recorded by the reader for the case. **BI-RADS:** Same as category recorded by the reader for the case. *From Initial Mammographic Findings form page.*
	One or more findings in this case	**POM:** Overall POM recorded by the reader for the case. **BI-RADS:** Overall category recorded by the reader for the case. *From Overall Patient Recall form page.*
One or more malignancies in this case[1,2]	No findings in this case	**POM:** Same as POM recorded by the reader for the case. **BI-RADS:** Same as category recorded by the reader for the case. *From Initial Mammographic Findings form page.*
	Findings in this case, but no findings matching the location(s) of any proven malignancies in this case	**POM: Assigned as the higher of 0 or, for readers who do not assign POM 0 to any case in a reading modality, the minimum POM score assigned by that reader in that modality.** **BI-RADS: Assigned as category one (1).**
	One or more findings correctly matching the location(s) of **any** proven malignancies in this case	**POM:** Highest POM score recorded by the reader for any of these matched findings. **BI-RADS:** Highest category recorded by the reader for any of these matched findings.

[1]If the case contains more than one malignant lesion, the reader will get credit for identifying the case as having one or more proven malignancies even if the reader does not identify all of the proven malignancies in the case. For example in a bilateral case, the reader would get credit for identifying the case even if the reader marks findings in only one breast.
[2]The POM scores and BI-RADS categories for any reader findings in this case that do not match the location(s) of any proven malignancies will be ignored in the per-subject analysis, which requires a single POM score and single BI- RADS category per subject conditional on whether the subject does or does not have proven malignancies.

Table 2. Per-Subject Recall Scores Requiring Correct Lesion Localization

Reference standard	Reader's interpretation	Per-Subject Recall Score
No malignancies in this case	No recall	Same as recall recorded by the reader for the case, that is, no recall.
	Recall	Same as recall recorded by the reader for the case, that is, recall.
One or more malignancies in this case[1]	No recall	Same as recall recorded by the reader for the case, that is, no recall.
	Recall and Findings in this case, but no findings matching the location(s) of any proven malignancies in this case	**Assigned as no recall.**
	Recall and One or more findings correctly matching the location(s) of any proven malignancies in this case	Same as recall recorded by the reader for the case overall.

[1]If the case contains more than one malignant lesion, the reader will get credit for recalling the case even if the reader does not identify all of the proven malignancies in the case. For example in a bilateral case, the reader would get credit for recalling the case even if the reader marks findings in only one breast as long as the overall decision is to recall the subject.

4.6. Analysis of Study Endpoints and Important Subgroups

4.6.1. Primary Endpoint

The primary endpoint on this study is non-inferior per-subject average AUC requiring correct lesion localization. We will estimate AUCs for each reader in each review condition (FFDM, DBT plus S-View) based on per-subject POM scores requiring correct lesion localization derived as in **Section 4.4**, above. The non-inferiority margin for this endpoint is delta = 0.05.

Primary analysis will not involve pooling across study radiologists, to allow for heterogeneity across them. We will provide graphs of each reader's ROC curve for each review condition. For each reader, the non-parametric (trapezoidal) AUC for the FFDM read, the DBT plus S-View read, and the difference between them, will be presented. Statistical inferences will account for correlations arising from having all study readers interpret all study cases. We plan to compare AUCs between reading conditions using the standard MRMC analysis of variance (ANOVA) method of Obuchowski and Rockette[1,2], to ensure generalization of the study results to both the population of readers and the population of cases. Two-sided 95% CIs will be used to quantify uncertainty in the within-modality estimates and the between-modalities differences.

Information on the magnitude and direction of differences between AUCs for the two modalities, and variance components and correlations that influence sample sizes and case mix for the pivotal reader study comparing AUCs between the two modalities, will be obtained from this MRMC analysis.

4.6.2. Secondary Endpoints

The following secondary endpoints will be explored in this pilot study, in order to best plan for the secondary endpoints for the pivotal study. Per-subject recall, BI-RADS, and POM scores requiring correct lesion localization will be derived as described in **Section 4.4**. Analyses of secondary endpoints also will be performed using standard MRMC ANOVA methods[1, 2], with two-sided 95% CIs used to quantify uncertainty. The secondary endpoints are:

1. Superior per-subject average AUC for DBT plus S-View versus FFDM.
2. Non-inferior and/or superior (lower) per-subject average recall rate for all non-cancer cases for DBT plus S-View versus FFDM, using non-inferiority margin delta = 0.05.

3. Superior per-subject average specificity for DBT plus S-View versus FFDM, based on BI-RADS scores.

4. Non-inferior and/or superior per-subject average sensitivity for DBT plus S-View versus FFDM, using non-inferiority margin delta = 0.10.

5. Non-inferior per-subject average recall rate for DBT plus S-View versus FFDM for all cancer cases, using non-inferiority margin delta = 0.10.

4.6.3. Important Subgroups

If performed, analyses in important subgroups also would employ standard MRMC ANOVA methods[1,2], with two-sided 95% CIs used to quantify uncertainty. The subgroup of soft tissue lesions (masses with or without calcifications, focal asymmetries, and/or architectural distortions) includes a cancer case with two malignant masses in the right breast. To account for this clustering, prior to the MRMC ANOVA we would use Rao and Scott's[3] method for clustered data to estimate sensitivity and Obuchowski's[4] extension of this to estimate the variance-covariance matrix of all possible pairs of sensitivities across readers and review conditions.

4.7. Test Reproducibility

Test reproducibility will not be evaluated on this pilot MRMC study.

4.8. Interim Analyses

No interim analyses of study endpoints are planned.

4.9. Safety Monitoring Analyses (Adverse Events)

No adverse events are anticipated on this pilot MRMC study using retrospective cases for which medical management has already been planned and carried out. Readers also are unlikely to report any adverse events. Any adverse events that are reported to BCL will be described.

4.10. Sample Size Calculations (Obtaining Parameters)

Parameters to use in sample size calculations for the pivotal study will be obtained from analysis of AUCs. The magnitude and direction of differences between AUCs the DBT plus S-View read compared with the FFDM read, and variance components and correlations that influence sample sizes for the pivotal reader study comparing them, will be obtained from MRMC analysis. In particular, we will obtain estimates of average AUC within each modality,

σ^2_b, σ^2_{ab}, r_1, r_2, r_3 (all defined below), and r_b, the correlation between the set of AUCs in the two (2) modalities.

Modeling Framework: Let A_{ij} be an estimate of the AUC in modality i (i = 1 for FFDM, 2 for DBT plus S-View) for the j^{th} radiologist (j = reader 1, …, J for J = 6). We consider the effects of radiologists to be random, because interest extends beyond the radiologists on this study to a larger population of potential radiologists from which these radiologists are a sample. Obuchowski and Rockette[1] model these estimates using mixed effects ANOVA, as

$$A_{ij} = \mu + \alpha_i + b_j + (\alpha b)_{ij} + e_{ij}$$

where

- μ is the overall AUC across the populations of readers and cases,
- α_i is the fixed effect of modality,
- b_j is a random effect for reader with expectation 0 and variance σ^2_b with random effects for different readers independent of each other,
- $(\alpha b)_{ij}$ is a random effect for the interaction of modality and reader with expectation 0 and variance σ^2_{ab} also with random effects for different readers independent of each other, and
- e_{ij} is random error with expectation 0, variance $\sigma^2_c + \sigma^2_w$, and covariance
    - $r_1\sigma^2_c$ for two AUCs from the same reader in different modalities,
    - $r_2\sigma^2_c$ for two AUCs from different readers in the same modality, and
    - $r_3\sigma^2_c$ for two AUCs from different readers in different modalities.

  The variance components σ^2_c and σ^2_w are case sample variance and within-reader variance, respectively.
- The random effects b_j, $(\alpha b)_{ij}$, and e_{ij} are independent of each other.
- When the readers review the case sample only once in each modality $(\alpha b)_{ij}$ and e_{ij} are not identifiable, and we cannot separate σ^2_{ab} from $\sigma^2_c + \sigma^2_w$.

Sample Size Estimation Framework: Power and required sample size to achieve it depend on the magnitude and direction of the difference in average AUC between DBT plus S-View and FFDM, $\hat{A}_2 - \hat{A}_1$, which we will estimate from this pilot study. Power also depends on the

number of cancer cases, number of non-cancer (benign, recalled, and normal) cases, and number of readers, J, through the variance of the difference[5]:

$$\mathrm{var}\left(\hat{A}_2 - \hat{A}_1\right) = \frac{2}{J}\{\sigma_{ab}^2 + \sigma_w^2 + \sigma_c^2[1 - r_1 + (J-1)(r_2 - r_3)]\}.$$

Numbers of cancer and non-cancer cases enter this variance through σ^2_c from a binormal approximation[6]. The closed-form expression for σ^2_c facilitates use when the ratio of non-cancer cases to cancer cases in the study being planned may differ from that ratio in the pilot study from which estimates of other parameters are obtained. We will use data from this pilot study to estimate the variance components and correlations in $\mathrm{var}\left(\hat{A}_2 - \hat{A}_1\right)$. To be conservative, the component σ^2_{ab} will be estimated as $\sigma^2_b \times (1 - r_b)$ when the unbiased estimate from ANOVA is negative.

4.11. Data Quality Review

Study database. Data for truthing, readings, and lesion matching on protocol FMSU2017-002A will be provided to BCL following approved data transfer specifications, to be developed by Fujifilm's study data vendor (Prosoft Clinical, Wayne, PA). *Analysis data: Subject level* will be a subset of protocol FMSU2013-004A *Analysis data: Subject level* in the archive generated by BCL for that study. Fujifilm will transfer reader experience data directly to BCL in comma-separated values (CSV) format.

Review and queries. BCL will examine the database for complete data and, if any data points are missing, query Fujifilm regarding reasons for this missingness. BCL also will verify that data values fall in allowable ranges and follow logical flow, and query Fujifilm regarding any exceptions. Fujifilm will resolve any such issues in the database, and provide responses and an updated database to the statistician. BCL will review the replies and updated database, and declare the data "all clean" if BCL determines that all queries have been resolved sufficiently for analysis to proceed. If data are not "all clean", BCL will query any remaining exceptions and Fujifilm will reply as above. Data will be locked only after BCL declares the database all clean.

BCL will use this final study database for all final study analysis. Final study analysis may be delayed until the study database is locked.

Missing Responses, Indeterminate Results, and Outliers. BCL will review the reasons for any missing data to evaluate whether the missingness is most likely missing completely at random,

missing at random, or systematic. BCL will determine appropriate methods for handling the missing data based on this evaluation and the amount of missingness. If BCL needs to amend this SAP to include more details for handling missing data, we will add these details before carrying out the analysis. In particular, if statistical models are used to address missing data issues these models and their assumptions will be explained clearly, and robustness of results will be explored.

The eCRFs are designed to prevent indeterminate responses; if any do occur, BCL will work with Fujifilm to resolve the issue. Regarding outliers the only continuous variable in the dataset is POM, a subjective ordinal variable for which each reader is permitted to use the full range on each case independent of values of other variables, such that no value of POM in 0 – 100% will be categorized as an outlier.

5. Results to be Reported

- *Dates (timeline).*
    - When cases were accrued on protocol FMSU2013-004A.
    - When cases were selected for the reader study.
    - When the readers' interpretations occurred.
    - When lesion matching occurred.
- *Clinical and demographic characteristics of cases.* For example: age, race, ethnicity, breast composition (BI-RADS breast density categories), study center, reference standard status (cancer, benign, recall, normal); and for cancers lesion type (mass, asymmetry, calcification, architectural distortion, other, or combinations thereof) and size (as determined on protocol FMSU2013-004A).
- *Clinical and demographic characteristics of readers.* For example: years in practice, whether the reader had specialized mammography training, number of mammograms read in the past year, percent of current practice that is mammography, usual hours spent in a clinical day (to address issues of reading fatigue), and whether or not they use C-View.
- *Flow diagram.* Reasons for any exclusions (for example, protocol deviations). If exclusions are minimal, this diagram may be omitted and replaced by text.
- *Summaries and cross-tabulations.*

- Table of number of findings by reference standard status and modality for each study reader.
- Means and SDs, and/or medians and quartiles or ranges, of POM requiring correct lesion localization by reference standard status and modality for each study reader.
- Table of BI-RADS requiring correct lesion localization by reference standard status and modality for each study reader.
- Table of recall requiring correct lesion localization by reference standard status and modality for each study reader.

- *AUC (primary endpoint).*
  - Graphs of the readers' non-parametric (trapezoidal) ROC curves based on per-subject POM scores requiring correct lesion localization for each review condition (FFDM read, DBT plus S-View read).
  - Table of corresponding AUCs for FFDM, DBT plus S-View, and the pairwise differences between them.
  - Average across readers of within-modality AUCs and between-modalities differences in AUCs.
  - Two-sided 95% CIs to quantify uncertainty in the within-modality estimates and the between-modalities difference.
  - Corresponding rotated forest plots and/or stacked bar charts (optional).
- *Recall rate for non-cancer cases, specificity, sensitivity, recall rate for cancer cases (secondary endpoints).*
  - Table of readers' estimates for FFDM, DBT plus S-View, and the pairwise differences between them.
  - Average across readers of within-modality estimates and between-modalities differences in between them.
  - Two-sided 95% CIs to quantify uncertainty in the within-modality estimates and the between-modalities difference.
  - Corresponding rotated forest plots and/or stacked bar charts (optional).

- *Performance metrics in important subgroups.*
    - *AUC only:* Graphs of the readers' non-parametric (trapezoidal) ROC curves based on per-subject POM scores requiring correct lesion localization for each review condition (FFDM read, DBT plus S-View read).
    - Table of readers' estimates for FFDM, DBT plus S-View, and the pairwise differences between them.
    - Average across readers of within-modality estimates and between-modalities differences in estimates.
    - Two-sided 95% CIs to quantify uncertainty in the within-modality estimates and the between-modalities difference.
    - *AUC only:* Corresponding rotated forest plots and/or stacked bar charts (optional).
- *Adverse events.* None are expected; any that are reported to BCL will be described.
- *Sample size.*
    - Magnitude and direction of difference between average AUC for DBT plus S-View and average AUC for FFDM.
    - Estimates of variance components and correlations that influence sample sizes and case mix for the pivotal reader study: $\hat{\sigma}_{ab}^2$ for interaction of reader and modality (DBT plus S-View or FFDM), $\hat{\sigma}_w^2$ for within-reader variance, $\hat{\sigma}_c^2$ for variance because cases are a sample, $\hat{r}_1$ for the correlation between AUCs from the same reader between modalities, $\hat{r}_2$ for the correlation between AUCs from different readers in the same modality, and $\hat{r}_3$ for the correlation between AUCs from different readers between modalities.

6. Regulatory and Administrative Information

If requested, BCL will provide an electronic copy of line data and associated metadata to Fujifilm. Also upon request, BCL will provide an electronic copy of statistical software code and/or its output for use in regulatory review, under the conditions of the contract between BCL and Fujifilm.

Analyses will be performed using R version 3.4.1 or later (2017-06-30; R Foundation for Statistical Computing, https://www.R-project.org) and cross-validated by standard BCL quality control methods.

7. References

[1] Obuchowski, NA, Rockette, HE. Hypothesis testing of diagnostic accuracy for multiple readers and multiple tests: An ANOVA approach with dependent observations. *Communications in Statistics, Part B: Simulation and Computation* 1995; 24:285-308.

[2] Hillis SL. A comparison of denominator degrees of freedom methods for multiple observer ROC analysis. *Statistics in Medicine* 2007; 26:596-619.

[3] Rao JNK, Scott AJ. A simple method for the analysis of clustered binary data, *Biometrics* 1992; 48:577-585.

[4] Obuchowski NA. On the comparison of correlated proportions for clustered data. *Statistics in Medicine* 1998; 17(13):1495-507.

[5] Obuchowski, NA. Multireader, multimodality receiver operating characteristic curve studies: hypothesis testing and sample size estimation using analysis of variance with dependent observations. *Academic Radiology* 1995 2(S1):S22-S29.

[6] Obuchowski NA. Computing sample size for receiver operating characteristic studies. *Investigative Radiology* 1994; 29:238–243.

Appendix 1

Case Report Forms (CRFs)

(CRFs follow)

FUJIFILM
Value from Innovation

FUJIFILM Medical Systems U.S.A., Inc.
419 West Avenue
Stamford, Connecticut 06902-6343
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FujifilmUSA.com

RADIOLOGIST READER QUESTIONNAIRE

Protocol Number(s):	FMSU2017-002A
1. Name:	
2. How many years have you been reading mammograms?	
3. In your most recent MQSA report, how many cases did you review in a year?	
4. How many hours do your read in an average clinic day?	
5. How many years have you been reading FFDM images?	
6. How many months/years have you been reading DBT images?	
6a. What DBT manufacturer do you regularly use?	
6b. What percentage of mammography cases do you perform with DBT?	
6c. If not 100%, what criteria do you use to decide which patients are imaged with DBT?	
6d. Do you use synthetic 2D with DBT?	
6e. If so, what percentage of mammography cases do you use synthetic 2D for?	
7. With respect to this reader study, what changes to the training program would you suggest?	
8. Please describe your overall impression of the reader study.	
9. Please describe any changes you would suggest to the overall reader study.	

FMSU2017-002 _Reader Questionnaire_20171031

10. Please describe your overall impression of the image quality of the FFDM mammograms.	
10a. Please describe any changes you would suggest to the image quality of the FFDM mammograms.	
11. Please describe your overall impression of the image quality of the DBT images.	
11a. Please describe any changes you would suggest to the image quality of the DBT images.	
12. Please describe your overall impression of the image quality of the S-View images.	
12a. Please describe any changes you would suggest to the image quality of the S-View images.	
13. Please describe your overall impression of the Bellus II Workstation?	
14. Please describe any changes you would suggest to the Bellus II Workstation?	
15. Please describe your overall impression of the travel arrangements/accommodations.	
16. Any additional comments:	

FMSU2017-002 _Reader Questionnaire_20171031

FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2013-004A
EDMS No.: IQG-0031788-D

Subject ID #: ☐☐☐-☐☐☐ Subject Initials (F/M/L): ☐☐☐

SUBJECT DEMOGRAPHICS AND INCLUSION/EXCLUSION CRITERIA

1. **Date of Consent (mm/dd/yy):** ☐☐-☐☐-☐☐
2. **Age of Subject:** ☐☐ 3. **Date of Birth (mm/dd/yy):** ☐☐-☐☐-☐☐
4. **Ethnicity:** ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown/Not Reported
5. **Race:** ☐ American Indian or Alaska Native ☐ Black or African American ☐ Asian ☐ Native Hawaiian or other Pacific Islander ☐ White ☐ Other: _____
6. **Subject enrolled as** *(check one)*: ☐ **Screening** ☐ **Diagnostic** ☐ **Recall**
7. **Inclusion Criteria:** (Subject may not be enrolled if any criteria are answered as "no")

		Yes	No	N/A
a)	For the screening-group subjects, is the subject at least 40 years of age, asymptomatic, and scheduled for a routine screening mammogram?	☐	☐	☐
b)	For the diagnostic-group subjects, is the subject at least 18 years of age; Scheduled for a biopsy due to an assessment of BI-RADS® 4 or 5 after diagnostic work-up of a suspicious screening or clinical finding within the last 60 days.	☐	☐	☐
c)	For the recall–group subjects, is the subject at least 18 years of age; Received a BIRADS 0 within the last 60 days, and are recalled for additional imaging.	☐	☐	☐
d)	Have the ability to understand the requirements of the study, to provide written informed consent, and to comply with the study protocol	☐	☐	
e)	Meet none of the exclusion criteria	☐	☐	

8. **Exclusion Criteria:** (Subject may not be enrolled if any criteria are answered as "yes")

		Yes	No
a)	Presence of an Implant	☐	☐
b)	Women with only a single breast; for example, post mastectomy patients.	☐	☐
c)	Is pregnant or believes she may be pregnant.	☐	☐
d)	A woman who has delivered and who has expressed the intention to breast-feed or is currently breast-feeding.	☐	☐
e)	A woman who has significant existing breast trauma within the last one (1) year.	☐	☐
f)	Has self-reported severe non-focal or bilateral breast pain affecting subject's ability to tolerate digital mammography and/or breast tomosynthesis examinations.	☐	☐
g)	A woman who has had a mammogram performed for the purpose of therapy portal planning within the last one (1) year.	☐	☐
h)	Cannot, for any known reason, undergo follow-up digital mammography and/or breast tomosynthesis examinations (where clinically indicated) at the participating institution.	☐	☐
i)	Is an inmate (see US Code of Federal Regulations 45CFR46.306)	☐	☐

FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2013-004A
EDMS No.: IQG-0031788-D

Subject ID #: ☐☐☐-☐☐☐ Subject Initials (F/M/L): ☐☐☐

MAMMOGRAPHIC FINDINGS

1. **Breast Density** *(check one):*

☐ a. Mostly Fatty ☐ b. Scattered Fibroglandular
☐ c. Heterogenously Dense ☐ d. Extremely Dense

2. **Routine Mammogram BIRADS Score** *(check one):*

☐ 0. ☐ 1 ☐ 2 ☐ 3
☐ 4a ☐ 4b ☐ 4c ☐ 5

3. **Does this patient have findings that require work-up?** ☐ Yes ☐ No
If YES, please complete a Lesion CRF for each lesion being evaluated.

FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B

Truther Form

Subject ID #: ☐☐☐ ☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

LESION #1

1. Image Type: ☐ FFDM ☐ DBT plus S-View

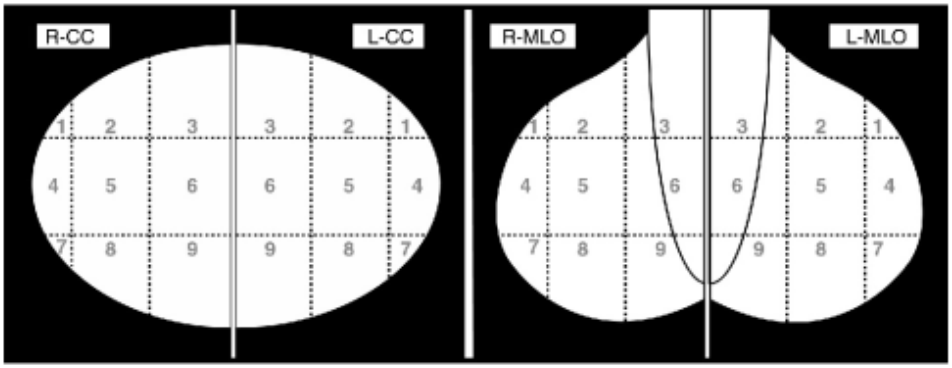
2. Affected breast: ☐ Right ☐ Left

3. What is the most suspicious finding type? *(check all that apply)*:

   a. ☐ Mass b. ☐ Asymmetry c. ☐ Calcification

   d. ☐ Architectural Distortion e. ☐ Other *(please specify)*: ☐

4 - 7. Mark an X at the location(s) of the lesion on the Mammogram:



4. ☐☐☐☐ 5. ☐☐☐☐ 6. ☐☐☐☐ 7. ☐☐☐☐

8. Lesion Location: N/A ☐ CC: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

   N/A ☐ MLO: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

9. Comments:

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FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B

Truther Form

Subject ID #: ☐☐☐ ☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

LESION #2 N/A ☐

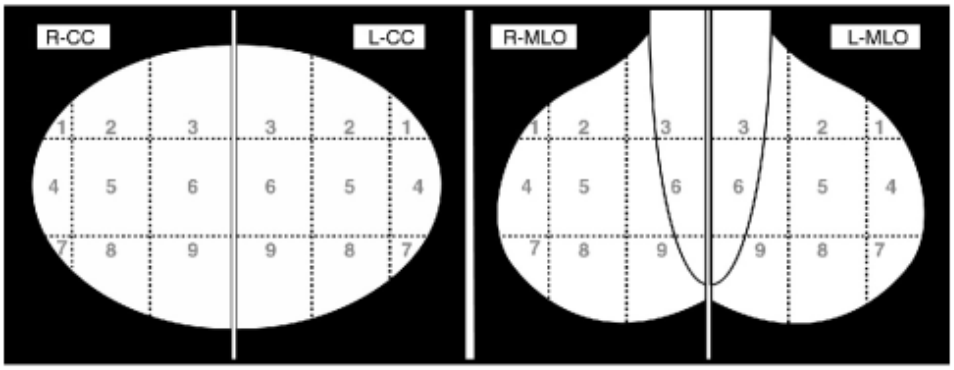
10. Affected breast: ☐ Right ☐ Left

11. What is the most suspicious finding type? *(check all that apply)*:

a. ☐ Mass b. ☐ Asymmetry c. ☐ Calcification

d. ☐ Architectural Distortion e. ☐ Other *(please specify)*: ☐

12 - 15. Mark an X at the location(s) of the lesion on the Mammogram:



12. ☐☐☐☐ 13. ☐☐☐☐ 14. ☐☐☐☐ 15. ☐☐☐☐

16. Lesion Location: N/A ☐ CC: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

N/A ☐ MLO: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

17. Comments:

☐

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FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B **Truther Form**

Subject ID #: ☐☐☐ ☐☐☐ **Date of Reading (mm/dd/yy):** ☐☐-☐☐-☐☐

LESION #3 N/A ☐

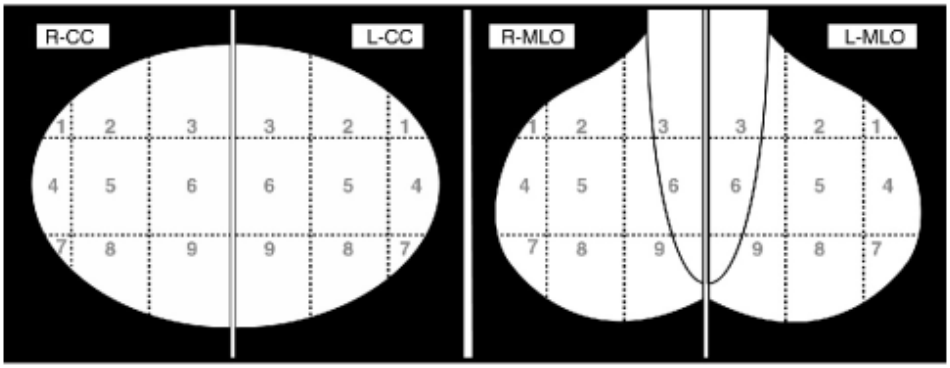
18. Affected breast: ☐ **Right** ☐ **Left**

19. What is the most suspicious finding type? *(check all that apply):*

a. ☐ Mass b. ☐ Asymmetry c. ☐ Calcification

d. ☐ Architectural Distortion e. ☐ Other *(please specify)*: ☐

20 - 23. Mark an X at the location(s) of the lesion on the Mammogram:



20. ☐☐☐☐ **21.** ☐☐☐☐ **22.** ☐☐☐☐ **23.** ☐☐☐☐

24. Lesion Location: **N/A** ☐ **CC: X** ☐☐☐ **Y** ☐☐☐ **Slice (DBT Only)** ☐☐☐

N/A ☐ **MLO: X** ☐☐☐ **Y** ☐☐☐ **Slice (DBT Only)** ☐☐☐

25. Comments:

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FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B

Reader Study Form

Sequence ID #: ☐☐☐ ☐☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

WRKSTNID #: ☐☐☐

INITIAL MAMMOGRAPHIC FINDINGS

1. Are there any mammographic findings in this patient's exam? ☐ Yes ☐ No

2. Initial BI-RADS Score: ☐ 0 ☐ 1 Negative ☐ 2 Benign Finding

3. If BI-RADS 1 or 2, please answer questions 3a and 3b:

3a. Overall, what is your estimated probability of malignancy for this patient (0-100%)? ☐☐☐

3b. Would you recall this subject? ☐ Yes ☐ No

If BI-RADS 0, please complete the following questions for up to 3 lesions:

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PROTOCOL: FMSU2017-002A/B

Reader Study Form

Sequence ID #: ☐☐☐ ☐☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

WRKSTNID #: ☐☐☐

LESION #1

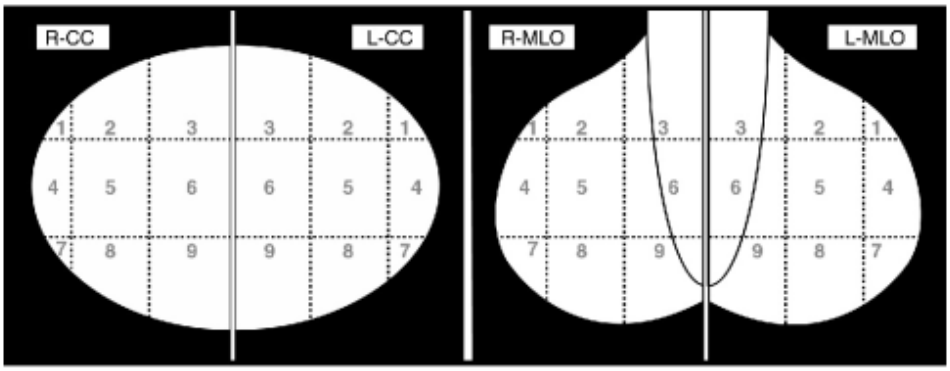
4. Affected breast: ☐ Right ☐ Left

5. What is the most suspicious finding type? *(check all that apply)*:

a. ☐ Mass b. ☐ Asymmetry c. ☐ Calcification

d. ☐ Architectural Distortion e. ☐ Other *(please specify)*: ☐

6 - 9. Mark an X at the location(s) of the lesion on the Mammogram:



6. ☐☐☐☐ 7. ☐☐☐☐ 8. ☐☐☐☐ 9. ☐☐☐☐

10. Lesion Location: N/A ☐ CC: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

N/A ☐ MLO: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

11. Based on the images reviewed, what is your forced BI-RADS score for this lesion? *(check one)*

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

12. What is your estimated probability of malignancy for this lesion (0-100%)? ☐☐☐

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PROTOCOL: FMSU2017-002A/B

Reader Study Form

Sequence ID #: ☐☐☐ ☐☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

WRKSTNID #: ☐☐☐

LESION #2 N/A ☐

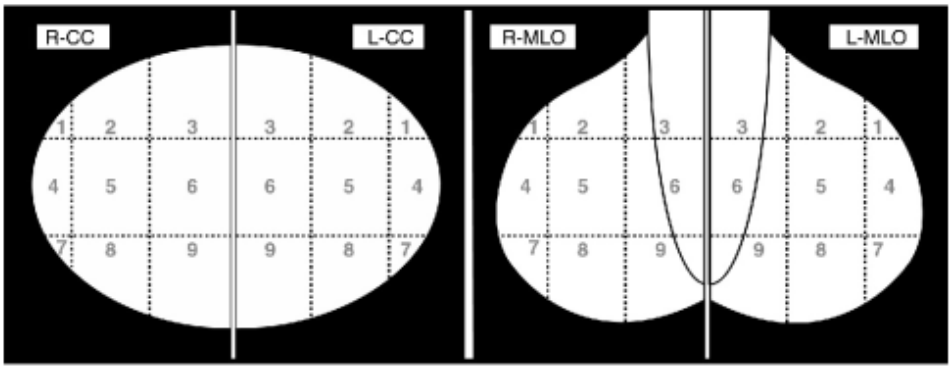
13. Affected breast: ☐ Right ☐ Left

14. What is the most suspicious finding type? *(check all that apply)*:

a. ☐ Mass b. ☐ Asymmetry c. ☐ Calcification

d. ☐ Architectural Distortion e. ☐ Other *(please specify)*: ☐

15 - 18. Mark an X at the location(s) of the lesion on the Mammogram:



15. ☐☐☐☐ 16. ☐☐☐☐ 17. ☐☐☐☐ 18. ☐☐☐☐

19. Lesion Location: N/A ☐ CC: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

N/A ☐ MLO: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

20. Based on the images reviewed, what is your forced BI-RADS score for this lesion? *(check one)*

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

21. What is your estimated probability of malignancy for this lesion (0-100%)? ☐☐☐

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FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B

Reader Study Form

Sequence ID #: ☐☐☐ ☐☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

WRKSTNID #: ☐☐☐

LESION #3 N/A ☐

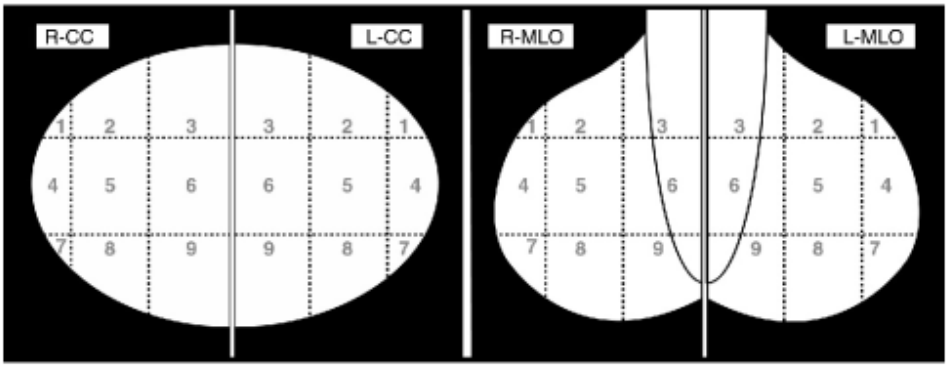
22. Affected breast: ☐ Right ☐ Left

23. What is the most suspicious finding type? *(check all that apply)*:

a. ☐ Mass b. ☐ Asymmetry c. ☐ Calcification

d. ☐ Architectural Distortion e. ☐ Other *(please specify)*: ☐

24 - 27. Mark an X at the location(s) of the lesion on the Mammogram:



24. ☐☐☐☐ 25. ☐☐☐☐ 26. ☐☐☐☐ 27. ☐☐☐☐

28. Lesion Location: N/A ☐ CC: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

N/A ☐ MLO: X ☐☐☐ Y ☐☐☐ Slice (DBT Only) ☐☐☐

29. Based on the images reviewed, what is your forced BI-RADS score for this lesion? *(check one)*

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

30. What is your estimated probability of malignancy for this lesion (0-100%)? ☐☐☐

FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B

Reader Study Form

Sequence ID #: ☐☐☐ ☐☐☐☐

Date of Reading (mm/dd/yy): ☐☐-☐☐-☐☐

WRKSTNID #: ☐☐☐

OVERALL PATIENT RECALL

31. Overall, would you recall this subject? ☐ Yes ☐ No

32. Overall, what is your forced BI-RADS score for this subject? *(check one)*

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

33. Overall, what is your estimated probability of malignancy for this subject (0-100%)? ☐☐☐

FUJIFILM Medical Systems U.S.A., Inc.

PROTOCOL: FMSU2017-002A/B

Lesion Matching Form

Subject ID #: ☐☐☐ ☐☐☐

Date of Review (mm/dd/yy): ☐☐-☐☐-☐☐

1. Image Type: ☐ FFDM ☐ DBT plus S-View
2. Reader Sequence Number: ☐☐☐ ☐☐☐☐
3. Truther Lesion #1:

   Reader Lesion #: ☐ 1 ☐ 2 ☐ 3 ☐ Not Seen
4. Truther Lesion #2 or ☐ NA:

   Reader Lesion #: ☐ 1 ☐ 2 ☐ 3 ☐ Not Seen
5. Truther Lesion #3 or ☐ NA:

   Reader Lesion #: ☐ 1 ☐ 2 ☐ 3 ☐ Not Seen
6. Comments:

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