SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Digital Breast Tomosynthesis Mammography System

Device Trade Name: ASPIRE Cristalle Digital Breast Tomosynthesis Option

Device Procode: OTE

Applicant's Name and Address: FUJIFILM Medical Systems U.S.A., Inc.
419 West Avenue
Stamford, Connecticut 06902

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160031

Date of FDA Notice of Approval: January 10, 2017

II. INDICATIONS FOR USE

The Fujifilm ASPIRE Cristalle with Digital Breast Tomosynthesis (DBT) Option acquires and generates FFDM and DBT images, and is intended for use in the screening and diagnosis of breast cancer.

A screening examination may consist of sets of CC and MLO images acquired in:

- the FFDM mode only, or
- an FFDM image set and a DBT image set acquired in the ST (standard) mode. The FFDM image set and the DBT image set must be acquired with N-mode dose setting, and may be acquired in one compression (Tomo Set mode) or separate compressions (FFDM and DBT modes).

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ASPIRE Cristalle Digital Breast Tomosynthesis Option labeling.

V. DEVICE DESCRIPTION

The Fujifilm ASPIRE Cristalle system (Model: FDR MS-3500) is an integrated digital mammography system. It consists of two main subsystems and has three operating modes.

A. Main subsystems

1) The FDR-3500DRLH X-ray Stand (Exposure Unit) is an integrated x-ray delivery system consisting of the FDR-3500H (exposure stand) and FDR-3000DRL (flat panel detector and control cabinet).

2) The FDR-3000AWS Acquisition Workstation (AWS) controls the exposure unit to acquire and process mammographic images. With it, the operator registers patient identifying information, selects exposure condition, displays study information, edits patient identifying information, displays studies and confirms image quality. The FDR-3000AWS is configurable with several monitor options.

B. Operation modes

The FDR MS-3500 has three selectable modes of operation. A single common detector and x-ray tube are used for all of the modes. The 1) full-field digital mammography (FFDM) mode is FDA-cleared (K133972) and is standard. This PMA is for two additional modes to be enabled upon FDA approval by a software upgrade and comprise the DBT Option: 2) the DBT mode and 3) the Tomosynthesis Set menu (Tomo Set menu) mode.

1) The standard FFDM mode produces conventional two-dimensional FFDM images of the breast. Both CC and MLO screening views and diagnostic views may be acquired at either the L- (Low), N- (Normal) or H- (High) mode dose setting.

2) The optional DBT mode captures the three-dimensional (3D) DBT images of the breast by taking multiple low-dose images per view along an arc over the breast. All images are acquired in the ST (standard) DBT mode with N-mode dose setting only. During acquisition, the x-ray tube moves approximately 1 degree for each image in a 15° arc (-7.5° to +7.5°) above the compressed breast, acquiring 15 images in approximately four (4) seconds. These acquired projection images are reconstructed for interpretation as cross-sectional “slices” of the breast, with each slice typically 1-mm thick. The DBT image set may be acquired for the CC, MLO and other views of the breast.

3) The optional Tomosynthesis Set menu (Tomo Set menu) mode combines the FFDM and DBT modes during a single compression of the breast, acquiring the DBT images in ST mode and N-mode dose and FFDM image with N-mode dose.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for breast cancer screening and diagnosis. These include clinical breast examination, film-screen mammography, full-field digital mammography, contrast enhanced spectral mammography, ultrasound, dedicated breast CT and magnetic resonance imaging.

The Hologic Selenia Dimensions 3D System, the GE SenoClaire, and the Siemens MAMMOMAT Inspiration, approved by FDA via PMA P080003, PMA P130020, and PMA P140011 respectively, can also produce DBT images.

After detection of an abnormality, a biopsy and pathology examination may be performed to diagnose the cancer. Each alternative has its own advantages and drawbacks. Patients should fully discuss these alternatives with their physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The ASPIRE Cristalle DBT Option which is known outside of the United States (OUS) as the AMULET Innovality Tomosynthesis Option, has never been withdrawn from OUS marketing for reasons related to safety or effectiveness. The AMULET Innovality system has been marketed in Japan, Germany, France, Belgium, Italy, Spain, Portugal, United Kingdom, Poland, Netherlands, Israel, Sri Lanka, Morocco, Tunisia, Taiwan, Uruguay, South Africa, Malta, China, Thailand, Hungary, Denmark, Australia, Greece, Switzerland, Norway, Sweden, Turkey, Argentina, Ecuador, Columbia, Mexico, Bolivia, India, Australia, Singapore, Philippines, Myanmar, United Arab Emirates (UAE), Egypt, and Lebanon.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No serious adverse events were reported for the patients enrolled in the clinical study. However, potential adverse effects of any mammography system include or arise from:

- excessive breast compression
- excessive x-ray exposure
- electric shock
- infection
- skin irritation, abrasion, or open skin wound

One minor adverse event and no serious adverse event was reported for the patients enrolled in the clinical study. For more information on the minor adverse event that occurred in the clinical study, please see Section X below.

Failure of the device to perform as expected or failure of the physician to correctly interpret the images produced by the device may lead to improper patient management decisions. False positives could lead to additional exams that could result in a small risk of additional

discomfort and complications such as infection or bleeding if a biopsy were performed. The risk of a serious complication is extremely low. False negatives would not be recalled which may result in delay in diagnosis and progression of disease up until the next screening exam or interval diagnosis.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Physical Laboratory Studies

Where applicable to the assessment of the imaging characteristics of a digital breast tomosynthesis system, FUJIFILM Medical Systems U.S.A., Inc. (also referred to as the "applicant") followed the physical laboratory testing methods in the FDA guidance, *Class II Special Controls Guidance Document: Full-Field Digital Mammography System*. When applicable, the applicant followed the EUREF *Protocol for the Quality Control of the Physical and Technical Aspects of Digital Breast Tomosynthesis Systems (Version 1.0, March 2015)*, the applicant also performed physical performance testing to address the device characteristics and image reconstructions that are specifically applicable to DBT.

- Table 1. Physical Laboratory Testing (applicable to Tomosynthesis)
- Table 2. Modulation transfer function in projection image and reconstructed image
- Table 3. Average Glandular Dose (AGD)
- Figure 1. Relative in-plane MTF (ST mode, 100 µm pixel size)
- Figure 2. CDMAM phantom scoring (ST mode, 100 µm pixel size)

Table 1. Physical Laboratory Testing (applicable to Tomosynthesis)

Test	Purpose	Acceptance Criteria	Results
1. Sensitometric Response	Assess detector signal response versus radiation exposure level	Linearity of the digital value versus radiation exposure level	The output signal level is linear relative to exposure
2. Spatial Resolution • Projection MTF	A quantitative measure of the spatial resolution properties of the image acquisition system.	No criteria – System Characterization	Table 2. Modulation transfer function in projection image and reconstructed image
• Reconstructed Image In-Plane Resolution	A quantitative measure of the in-plane spatial resolution properties of the reconstructed image.	No criteria – Follow the ACR phantom evaluation	Figure 1. Relative in-plane MTF (ST mode, 100 µm pixel size)

Test	Purpose	Acceptance Criteria	Results
• Reconstructed Image Z-Resolution	A quantitative measure of the z-resolution properties of the reconstructed image.	10.0 mm ± 1.0mm	FWHM in 1shot Phantom M Plus 24x30 evaluated by Tomo QC Calculation Tool. The result was 10.0mm ± 1.0mm within the criteria.
3. Noise Analysis	A quantitative measure of the noise properties as described by the noise power spectrum (NPS) as a function of spatial frequency and exposure level	No criteria – System Characterization	NPS responds linearity to the exposure. It shows x-ray quanta noise is dominant.
4. Signal-to-Noise Ratio Transfer – DQE	A quantitative measure of the efficiency of signal-to-noise ratio (SNR) transfer by calculating the detective quantum efficiency (DQE) as a function of spatial frequency.	No criteria – System Characterization	DQE result shows it is almost constant from 0.01mGy to 0.04mGy.
5. Dynamic Range • NEQ	A quantitative measure of the noise properties as described by the noise equivalent quanta (NEQ) as a function of exposure level	Linearity of NEQ versus exposure level	NEQ is linear relative to exposure.
• DQE	A quantitative measure of the efficiency of signal-to-noise ratio (SNR) transfer by calculating the detective quantum efficiency (DQE) as a function of exposure level.	Almost constant	DQE is almost constant against exposure.
6. Fading	Not applicable -For systems using a delayed readout of image data	Not applicable	Image readout is accomplished immediately after x-ray exposure, therefore, fading testing is not applicable

Test	Purpose	Acceptance Criteria	Results
7. Repeated Exposure and Image Erasure Tests	Assessment of ghost on successive exposure	Ghost image factor should be below 0.3.	The ghost factor for ST mode was 0.06 well below 0.3. It was evaluated in accordance with EUREF 4th Edition.
8. Automatic Exposure Control Performance			
• AEC performance	A quantitative measure of Average Glandular Dose (AGD) as a function of breast thickness.	Not to exceed 3.0mGy per view with 4.2cm of 50% glandular and 50% adipose composition breast which is the MQSA limit for screening.	Table 3. Average Glandular Dose (AGD). Well below the MQSA limit.
• Phantom Testing - ACR MAP	Detectability of small structures in the breast	MQSA minimum requirement – Perfect phantom scores values are: 6, 5, 5. Passing phantom scores values are: 4, 3, 3.	Tomosynthesis scans using AEC (automatic exposure control) settings at W/Al anode/filter at 26, 30 and 33 kV, in 20mm, 42mm, and 60mm, respectively, were evaluated by a group of experienced human observers. The following are the average score values (100 µm pixel size): 5.8, 4.0, 4.5 at 20mm, 5.0, 4.0, 4.0 at 42mm and 4.8, 3.8, 3.8 at 60mm for fibers, speck groups, masses, respectively.

Test	Purpose	Acceptance Criteria	Results
• Phantom Testing - CDMAM	Detectability of contrast details of structures in the breast	No criteria – Evaluation of CDMAM is under discussing in the relevant society such as EUREF.	Figure 2. CDMAM phantom scoring (ST mode, 100 µm pixel size).
9. Patient Radiation Dose	A quantitative estimate of the patient radiation dose as the average glandular dose.	Not exceed 3.0mGy at 4.2 cm and 50% glandular and 50% adipose composition phantom in the cc- projection per MQSA requirements.	Tomosynthesis testing simulated 4.2cm thick compressed breasts consisting of 50 percent glandular and 50 percent adipose tissue. The measured AGD was 1.2 mGy for ST mode N-mode, well below the MQSA limit.
10. Breast Compression System	The minimum and maximum powered compression force	Current standard of care recommends that the maximum compression force be set to clinical parameters such as skin tautness, breast anchoring, patient tolerance, etc.	The measured compression force did not exceeded 200N, when 200N which is the maximum value which can be set was applied.
11. Geometric Distortion (Reconstructed Image)	Assess fidelity in the mapping of geometrical lengths inside individual slices	Not exceed ± 2% taking into account of geometric magnification.	The distortion was around 0.3%, well below the criteria.
12. Uniformity Reconstructed Slice with CNR	Grayscale uniformity inside individual slices is assessed using spatially homogeneous PMMA blocks	Within -30% relative to the CNR of ROI at the center of the chest wall side.	The minimum CNR was -16% (100 µm pixel size) within the criteria.

Test	Purpose	Acceptance Criteria	Results
13. Collimation Assessment/ Breast Support Alignment in Projection Mode	Assess x-ray exposure field	X-ray field extends to the edge of the patient support of chest wall side within 2mm. Does not extend to the edge of the patient support for other sides. -based on IEC 60601-2-45	The measured x-ray field was within the criteria.

Table 2. Modulation transfer function in projection image and reconstructed image

Spatial frequency	Projection image in-plane resolution	Reconstructed image in-plane resolution			
	150µm	100µm		150µm	
	of Horizontal and Vertical	Horizontal	Vertical	Horizontal	Vertical
1	0.89	0.94	0.65	0.90	0.62
2	0.75	0.63	0.09	0.64	0.09
3	0.39	0.20	0.02	0.31	0.02

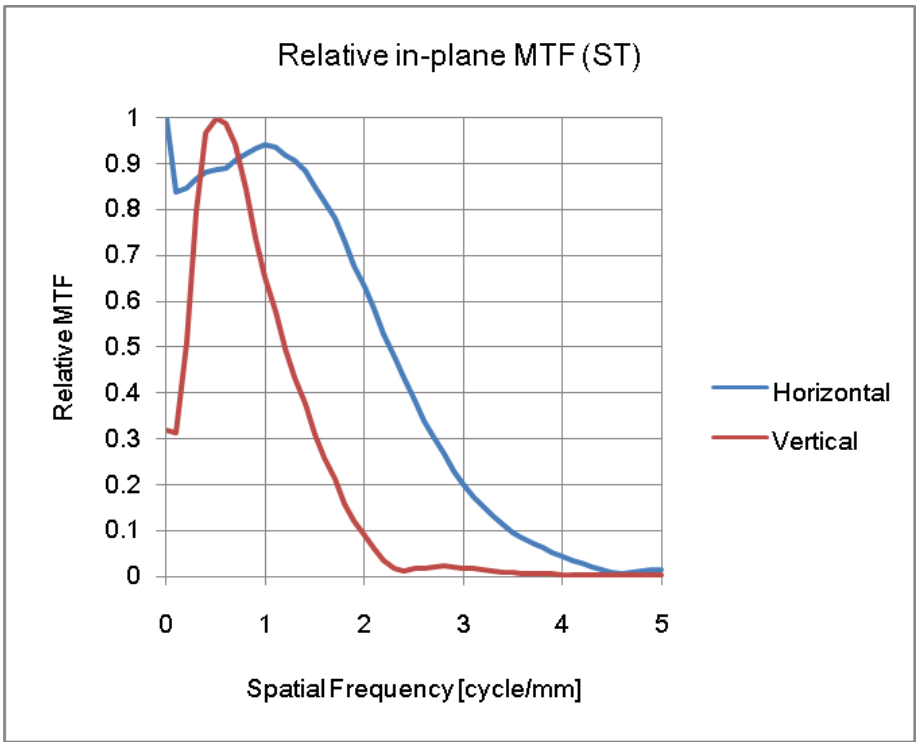


Figure 1. Relative in-plane MTF (ST mode, 100 µm pixel size)

Table 3. Average Glandular Dose (AGD)

PMMA Thickness (mm)	Tube Voltage (kV)	Tube Load (mAs)	AGD (mGy)
20 mm	26 kVp	36	1.0 mGy
30 mm	28 kVp	32	0.9 mGy
40 mm	30 kVp	40	1.3 mGy
45 mm	32 kVp	40	1.6 mGy
50 mm	33 kVp	42	1.7 mGy
60 mm	36 kVp	50	2.6 mGy
70 mm	37 kVp	63	3.2 mGy

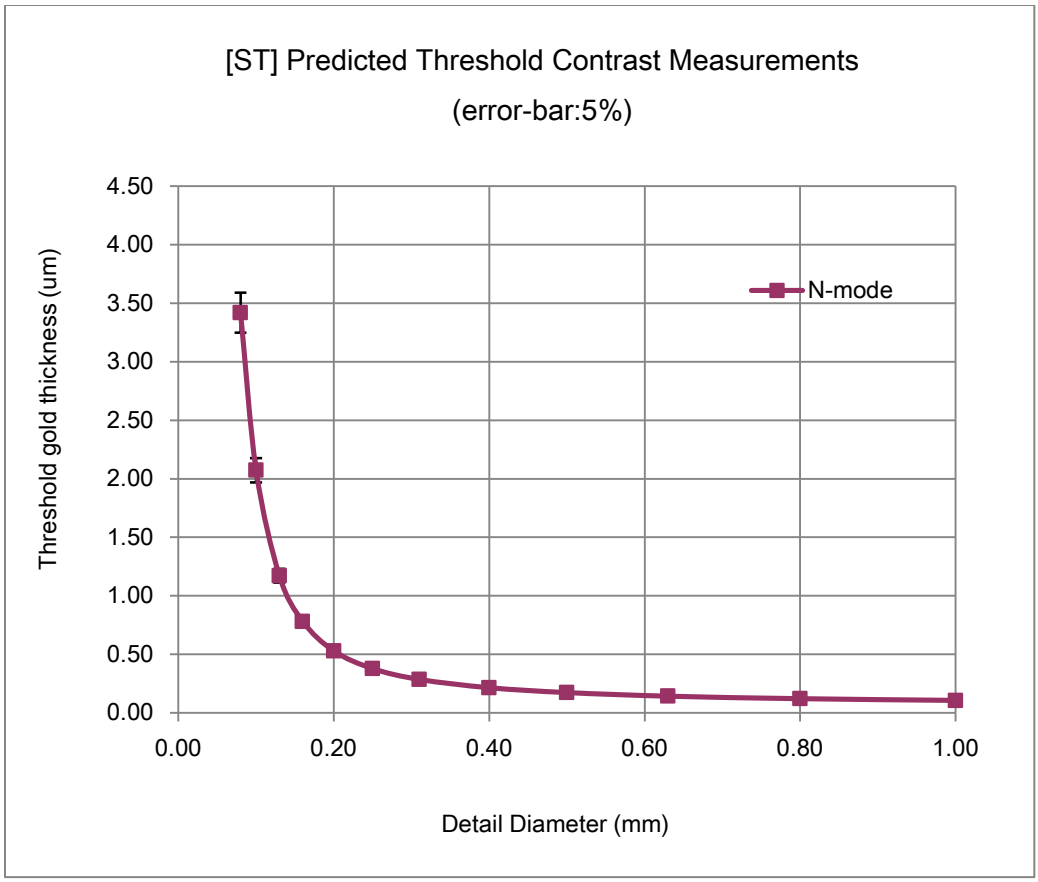


Figure 2. CDMAM phantom scoring (ST mode, 100 µm pixel size).

B. Additional Studies

Conformance to Voluntary Standards

The applicant provided certificates of conformance to the following voluntary standards:

- AAMI / ANSI ES60601-1:2005/(R)2012 And C1:2009/(R)2012 And, A2:2010/(R)2012
- IEC 60601-1-2 Edition 3: 2007-03
- IEC 60601-1-3 Edition 2.0 2008-01
- IEC 60601-2-45 Edition 3.0 2011-02
- ISO 10993-1 Fourth edition 2009-10-15
- IEC 62304 First Edition 2006-05
- ISO 14971 Second Edition 2007-03-01
- NEMA PS 3.1 - 3.20 (2011)

Software-Related Documentation

The applicant provided design and software testing documentation consistent with FDA's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* and *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices*. The applicant conducted software unit testing and integration testing to verify that all the sub-systems satisfy the software requirements and integrated successfully. System testing was also conducted to validate that the software specifications conform to its intended use and user requirements. The applicant conducted regression testing to ensure that new software features introduced by the tomosynthesis option do not create problems with previous version of the software. All the test activities were completed successfully. The impact of the unresolved anomalies on device safety and effectiveness were properly assessed. The mitigations for the unresolved anomalies were provided and acceptable.

C. Conclusion of Non-Clinical Studies

Physical laboratory testing and the conformance to the voluntary standards demonstrated that the ASPIRE Cristalle DBT option can be used to produce diagnostic quality DBT images.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed clinical studies to establish a reasonable assurance of safety and effectiveness of the ASPIRE Cristalle DBT Option for breast cancer screening and diagnosis in the US. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

A. Study Design

Patients were enrolled between June 30, 2014 and December 30, 2015. The studies included a prospective image acquisition study in which subjects were imaged with the investigational device in addition to their standard of care, and a retrospective multiple-reader multiple-case (MRMC) pivotal reader study.

Table 4. Clinical Studies

Study	Study Design	Study Objective	Number of Sites/ Readers	Number of Subjects	Clinicaltrials.gov Registration #
Image Acquisition	Prospective subject accrual	• Subject accrual for blinded reader studies • Evaluate the safety of the device	5 enrollment sites	1232 subjects	NCT02156258
Pivotal MRMC Study	Retrospective reader study	• Evaluate the safety and effectiveness of the device. • Establish that FFDM + DBT has superior diagnostic accuracy as compared to FFDM alone.	28 readers	300 cases (60 cancers, 49 benign biopsy cases, 72 recall subjects, and 119 normal cases)	NCT02692209

Prospective Case Accrual

The applicant designed and conducted a prospective case accrual study to collect FFDM and DBT images of patients undergoing either a routine screening mammogram, undergoing diagnostic work-up after a potential anomaly was detected at screening, or scheduled for a biopsy of a suspicious finding

A total of 1232 subjects were enrolled from five United States clinical trial sites under IRB approval for the image acquisition protocol entitled: FMSU2013-004A: "Acquisition of Digital Mammography and Breast Tomosynthesis Images for Clinical Evaluation of Fujifilm Digital Breast Tomosynthesis".

For all subjects, in addition to their standard of care imaging, mediolateral oblique (MLO) and craniocaudal (CC) DBT images were acquired followed immediately in the same compression by the acquisition of the FFDM image of the same breast view, for a total of eight images per subject. Both the FFDM and DBT images were collected in digital format by the applicant.

1. Clinical Inclusion and Exclusion Criteria
   Inclusion Criteria

   Subjects enrolled must have met all the following inclusion criteria:

   - Screening Subjects
     - Be at least 40 years of age, are
     - Asymptomatic,

    - Scheduled for a routine screening mammogram,
- Recall Subjects
    - Be at least 18 years of age,
    - Received a BIRADS 0 within the last 60 days
    - Are recalled for additional imaging
- Diagnostic Subjects
    - Be at least 18 years of age,
    - Had a screening mammogram within the last 60 days, been given a BI-RADS® 0 and are recalled for additional imaging and are given a BI-RADS® 4 or 5, or have had a four-view mammogram within the last 60 days for clinical concerns and been given a BI-RADS 4 or 5, and scheduled for biopsy.
- Have the ability to understand the requirements of the study, to provide written informed consent, and to comply with the study protocol, and
- Meet none of the exclusion criteria.

Exclusion Criteria

Subjects were excluded from participating in the study if they meet any one or more of the following exclusion criteria:

- Presence of a breast implant.
- Women with only a single breast; for example, post mastectomy patients.
- Is pregnant or believes she may be pregnant.
- A woman who had recently delivered and who has expressed the intention to breast-feed or is currently breast-feeding.
- A woman who has significant existing breast trauma within the last one year.
- Has self-reported severe non-focal or bilateral breast pain affecting subject's ability to tolerate digital mammography and/or breast tomosynthesis examinations.
- A woman who has had a mammogram performed for the purpose of therapy portal planning within the last year.
- Cannot, for any known reason, undergo follow-up digital mammography and/or breast tomosynthesis examinations (where clinically indicated) at the participating institution.
- Is an inmate (see United States Code of Federal Regulations 45CFR46.306)

2. Follow-up Schedule

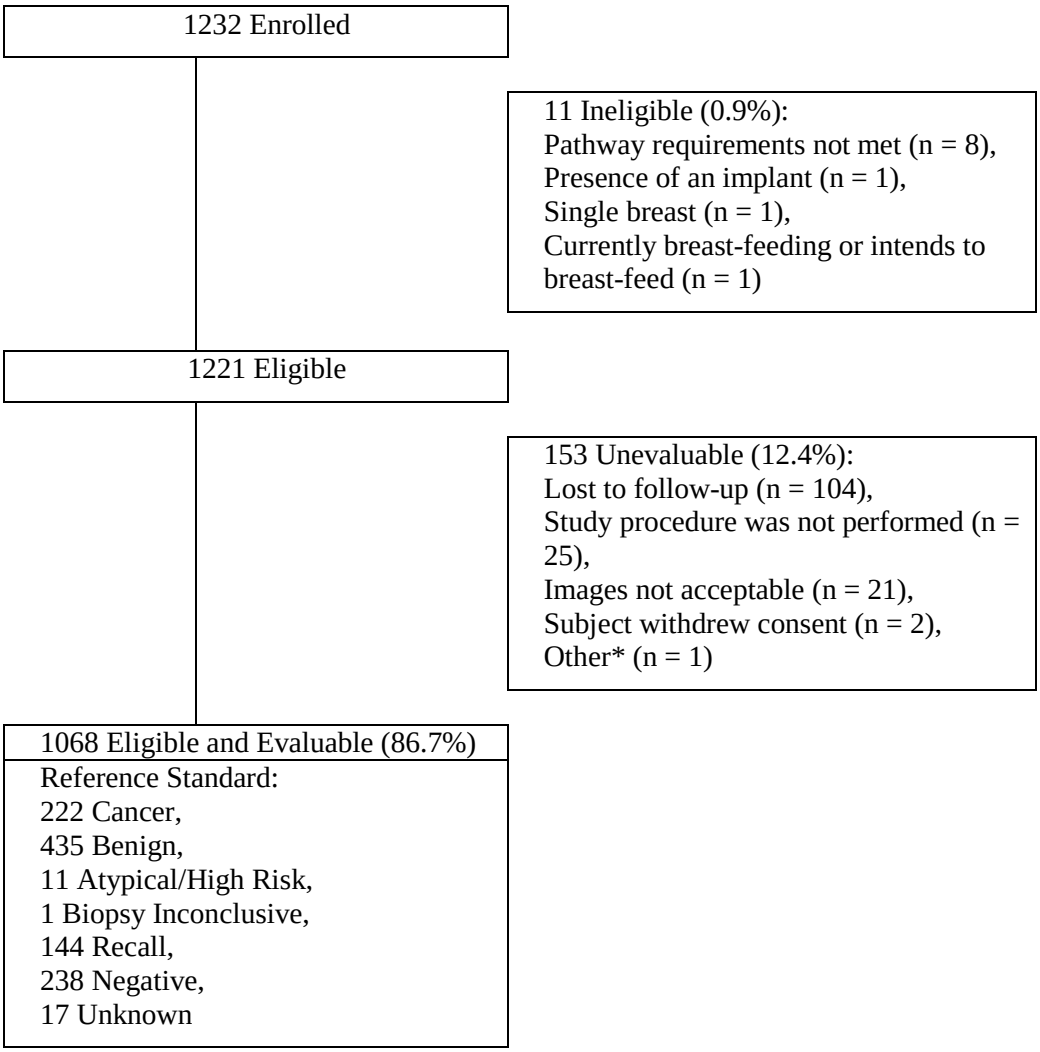
All patients with normal mammograms were asked to return for confirmatory standard of care mammograms at one year to confirm non cancer status. Subjects that underwent biopsies and had pathology results were not required to return one year later. The one year follow-up or pathology result determined the subject's final clinical diagnosis for the study. Subjects that had a negative/benign mammogram or benign biopsy were classified as having a final diagnosis of "no cancer". All cancer mammograms were confirmed by a biopsy proved pathology report. Discovery of a cancer at any time up to and including the one year examination resulted in the subject being assigned a final diagnosis of cancer.

3. Clinical Endpoints

Successful demonstration of the safety and effectiveness of the ASPIRE Cristalle DBT Option (Fujifilm DBT system) is defined as the per-subject average AUC for FFDM + DBT being statistically significantly superior to the average AUC for FFDM at statistical significance level alpha = 0.05, which is established if the lower limit of the two-sided 95% CI for the difference in average AUC for FFDM + DBT minus FFDM lies entirely above zero (0).

B. Accountability of PMA Cohort

At the time of database lock, a total of 1232 patients were enrolled on the image acquisition protocol. Eleven (11) subjects were ineligible (0.9%), and 153 eligible subjects were not evaluable (12.4%; Figure 3). The set of 1068 eligible and evaluable subjects includes 222 subjects with cancer (20.8%=222/1068). Eighty (80) of the eligible and evaluable Recall subjects and 17 of the eligible and evaluable Negative subjects are still being followed through one-year imaging (9.1%=97/1068). Among the Recall subjects 68 are within the 455 day follow-up window as of the last data transfer and 12 are overdue; among the Negative subjects these numbers are 3 and 14, respectively.



*Other reason for unevaluability: PATIENT CONSENTED ON 04/27/15, ADDITIONAL IMAGES WERE FROM OUTSIDE FACILITY PRIOR TO DATE OF ENROLLMENT (04/27/15)

Figure 3. Accountability of Subject Cohort: N

Pivotal MRMC Reader Study

The applicant designed and conducted a retrospective pivotal MRMC study using a unique enriched subset of cases accrued from the prospective image acquisition study. The objective of this study was to demonstrate the superiority of the FFDM + DBT to FFDM only for the detection of breast cancer.

Pivotal Study Cohort and Baseline Parameters

A total of 298 cases (59 cancer cases and 239 non-cancer cases) were randomly selected and included in this pivotal reader study from the library of FFDM and

DBT mammograms collected under the image acquisition protocol. All cancer cases were truthed. The 239 non-cancer cases were comprised of:

- 49 biopsy proven benign cases,
- 71 recall cases, and
- 119 normal cases.

Cases were randomly selected to avoid selection bias and to provide representative distributions of breast density, finding types, and equal distribution across enrolling sites. The case data included in this pivotal study were different than the cases used in the training cohort. The 191 normal and recall cases were selected and used in the reader study before the one year follow up on all cases were collected.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population in terms of breast density and cancerous lesion characteristics were typical of the United States screening population (see Tables 5, 6, and 7, below).

Table 5. Characteristics of Study Sample: N (%) unless otherwise noted

	Total (N = 298)
Site	
T01	84 (28%)
T02	57 (19%)
T03	50 (17%)
T04	55 (18%)
T05	52 (17%)
Enrollment Pathway	
Screening	120 (40%)
Recall	79 (27%)
Diagnostic	99 (33%)
Age	
Median (IQR)	56 (49 - 65)
Range	20 – 82
Mean (SD)	56.5 (10.7)
Race	
American Indian or Alaska Native	3 (1%)
Asian	1 (< 1%)
Black or African American	23 (8%)
White	269 (90%)
Other/Unknown*	2 (1%)
Ethnicity	
Hispanic or Latino	25 (8%)
Not Hispanic or Latino	268 (90%)
Unknown/Not Reported	5 (2%)
Breast Composition (Density)	
a. Almost entirely fatty	29 (10%)
b. Scattered areas of fibroglandular density	132 (44%)
c. Heterogeneously dense	115 (39%)
d. Extremely dense	22 (7%)
Number of Lesions	
0	117 (39%)
1	154 (52%)
2	22 (7%)
3	5 (2%)
Reference Standard Status	
Cancer	59 (20%)
Benign	49 (16%)
Recall	71 (24%)
Negative	119 (40%)

Header N applies unless otherwise provided. IQR = interquartile range, 25th percentile through 75th percentile. SD = standard deviation.
All subjects are Female.
*Race Other/Unknown = ITALIAN (n = 1), UNKNOWN (n = 1).

Table 6. Characteristics of Cancer Cases: N (%) unless otherwise noted

	Total (N = 59)
Histology	
IDC with DCIS (2 lesions)	1 (2%)
IDC (2 lesions)	2 (3%)
ILC (2 lesions)	1 (2%)
IDC; DCIS	2 (3%)
DCIS (2 lesions)	3 (5%)
IDC with DCIS	5 (8%)
IDC	19 (32%)
ILC	4 (7%)
DCIS	21 (36%)
Other*	1 (2%)
Size (mm, maximum)	
N	**55**
Median (IQR)	16.0 (10.0 - 23.0)
Range	2.0 - 90.6
Mean (SD)	19.03 (13.92)
Lesion Type(s)	
Soft Tissue Lesion(s) Only	28 (47%)
Soft Tissue Lesion(s) and Calcifications (separate and/or associated)	10 (17%)
Calcifications Only	21 (36%)

Header N applies unless otherwise provided. IQR = interquartile range, 25th percentile through 75th percentile. SD = standard deviation.
IDC = invasive ductal carcinoma. ILC = invasive lobular carcinoma. DCIS = ductal carcinoma in situ.
*Other histology = Papillary carcinoma cannot rule out invasion.

Table 7. Characteristics of Benign Cases: N (%) unless otherwise noted

	Total (N = 48*)
Size (mm, maximum)	
N	39
Median (IQR)	10.0 (7.0 - 14.0)
Range	3.0 - 57.0
Mean (SD)	12.91 (10.74)
Lesion Type(s)	
Soft Tissue Lesion(s) Only	24 (50%)
Soft Tissue Lesion(s) and Calcifications (separate and/or associated)	4 (8%)
Calcifications Only	20 (42%)

*Excludes one case for which we lack lesion information because this case is Benign based on a biopsy at one-year follow-up on the Image Acquisition protocol.
IQR = interquartile range, 25th percentile through 75th percentile. SD = standard deviation.

Reference Standard
The reference standard for a cancer case is a case in which at least one lesion is confirmed as malignant by biopsy or surgery.
The reference standard for a non-cancer case was biopsy, surgery, or interpretation by radiologists at the enrolling site:

- Biopsy proven non-cancer case
- Non-cancer case with reportable findings ("recall")
- Non-cancer case with no reportable findings ("normal")

Cancer cases: ground truth (GT) for the type and location of cancer cases were based on the mammography findings described by the radiologist at the clinical site and supported by the radiology and the pathology report from biopsy procedures. GT FFDM and DBT images with lesion locations marked electronically were created by an independent radiologist based on review of the electronic case report forms (eCRFs), radiology and pathology reports.

Readers
28 readers were involved in this pivotal study. The readers had a variety of experience ranging from breast imagers to general radiologists, with and without DBT experience, and represented academic and nonacademic institutions. Readers were board certified and MQSA-qualified.

Prior to the blinded reading session, all readers took part in a training, which provided an overview of DBT physics, the specific features of DBT, and the differences between FFDM and DBT. After being trained on the use and features of the ASPIRE Bellus workstation, the readers reviewed approximately 50 FFDM images with corresponding DBT images of various breast pathologies and densities with the training radiologist. Additionally, the flow of the sequential reading session (FFDM first, then FFDM + DBT) was explained as well as how interpretation data should be recorded in the eCRFs. The readers then independently interpreted 40 cases of various breast pathologies and densities. The training radiologist reviewed and provided direct feedback to the readers for these 40 cases. The readers then independently interpreted 60 cases of various breast pathologies and densities. No feedback was provided for this case set. None of the readers were excluded from the primary analysis since readers are not subjected to any cancer detection test in clinical practice.

Blinded Reading Sessions
The readers were told that the samples of cases do not represent a standard screening population, and were blinded to the actual distribution and nature of the set of images they were asked to review. Readers were masked to the results of the reference standard and image acquisition interpretations for each case. Readers did not have access to prior mammograms or other clinical information. All readers performed their interpretations independently.

Each study reader was randomly assigned to a unique reading order. All study readers interpreted all study cases in a sequential format, with FFDM only first and then FFDM + DBT. Readers interpreted the randomized preloaded mammograms in their assigned order.

Readers were assisted by scribes, who entered each reader's responses in the electronic reader case report forms. The reader completed the eCRFs for each case for the two reads. For each read, the reader first reported whether there were any reportable findings:

- If the answer to this question was "no" the reader was asked to choose for this case: a BI-RADS assessment category of either 1 or 2, and a Probability of Malignancy (POM) score following the POM guidance provided (see below) as reference (radiologists were allowed full range of POM scoring), and recall decision of "no".
- If the reader answered "yes" as to whether there were reportable findings, the reader was asked to confirm assignment of an initial BI-RADS assessment category of 0, and then provided detailed information on for up to three suspicious findings:
    - Location (including breast, view, quadrant locations and x/y/slice coordinates, if possible)
    - Type, as mass, asymmetric density, focal asymmetry, microcalcifications, other; Radiologist may check all that apply.
    - "Forced" BI-RADS assessment category 1, 2, 3, 4, or 5
    - POM score 0 through 100%
    - The reader was then asked for an overall: recall decision, forced BI-RADS assessment category, and POM score, for the case.

    A study monitor representing the sponsor reviewed the information recorded (eCRF's) for completeness.
    In cases with reportable findings, consistency of BI-RADS scores, POM scores, and recall decisions were not forced – e.g., readers were permitted to use the full range of POM scores for a finding (following the POM guidance) no matter what BI-RADS score they assigned to it.

    Probability of Malignancy (POM): POM is a 0 to 100 score assigned by readers to each suspicious finding, as their perception of the percentage chance that the suspicious finding might be malignant. To help the assignment of POM scores, readers were instructed to use the entire POM scale, with descriptions of POM values provided below as guidance:
    Note: POM scores were determined and analyzed separately from the BI-RADS score**.**

Table 8. Probability of malignancy (POM) guidance

POM Score (%)	Description
0-20	Negative/Benign
21–40	Probably benign
41–60	Possibly malignant
61–80	Probably malignant
81–100	Malignant

Statistical Methods for Primary Analysis

The primary endpoint, AUC, was estimated for each reader in each review condition (FFDM, FFDM + DBT) based on per-subject POM scores requiring correct lesion localization.

Primary analysis did not involve pooling across study radiologists, to allow for heterogeneity across them. Rather, each reader's empirical ROC curve were averaged to yield the overall comparison. For each reader, the non-parametric (trapezoidal) AUC for the FFDM read, the FFDM + DBT read, the difference between them, and the associated variance-covariance matrix were obtained using the method of DeLong, et al.[1] Statistical inferences accounted for correlations arising from having all study readers interpret same study cases. MRMC comparison of AUCs between the FFDM read and the FFDM + DBT read was performed using the mixed effects analysis of variance (ANOVA) method of Obuchowski and Rockette[2] with degrees of freedom updated as in Hillis.[3] Two-sided 95% confidence intervals (CIs) were used to quantify uncertainty.

Successful demonstration of the safety and effectiveness of the ASPIRE Cristalle DBT Option (Fujifilm DBT system) is defined as the average of per-subject AUC for FFDM + DBT being statistically significantly superior to the average AUC for FFDM at statistical significance level alpha = 0.05, which is established if the lower limit of the two-sided 95% CI for the difference in average AUC for FFDM + DBT minus FFDM lies entirely above zero (0).

Supportive analysis. Alternative free-response receiver operating characteristic (AFROC) curves, based on multiple reader findings per case, were used in supportive analysis of the primary aim.[6] MRMC jackknife AFROC (JAFROC) analysis employing the Dorfman, Berbaum, and Metz[4] method with Hillis updates,[5] and the weighted JAFROC (wJAFROC) figure of merit (FOM) with equal weight assigned to all malignant lesions within a cancer case, was performed. This analysis takes into account the correlations arising from having all study readers interpret all study cases.

Missing data: One-year follow-up. Primary analysis of AUC classified 37 of the 71 recall cases and 35 of the 119 negative cases without one-year negative follow-up as non-cancer cases, consistent with an interval cancer rate of 0.77 per 1000 screening exams and an expected number of interval cancers among these cases equal to 0.15.[8] A sensitivity analysis was performed to explore robustness of the results by re-classifying some of the recall and negative cases missing one-

year follow-up as cancer in a "worst case" AUC analysis. Plausible cancer rates (4.91 cancers per 1000 as an upper bound) and a predefined threshold on probability of number of cancers (0.001) were used to determine that at most 3 cases without negative one-year follow-up should be reclassified in the robustness analysis. These cases were selected as the ones with the lowest average POM scores for FFDM + DBT (worst case if these were actually cancer) across readers. The results of this analysis supported the robustness of the conclusions of the primary analysis.

Adverse Event

The analysis of safety was based on the 1232 enrolled subjects as of December 30, 2015. There was only one adverse event reported during the image acquisition study. One subject fainted during her study procedure. The enrolling center determined that the event was not related to the study procedure nor the investigational device. The subject fully recovered before leaving the clinical center

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 1216 enrolled patients as of December 31, 2016. There was only one adverse event reported during the image acquisition study. One subject fainted during her study procedure. It was determined by the enrolling center not to be related to the study procedure or investigational device.

Average Glandular Dose: With the addition of the DBT images to the standard FFDM screening procedure, the radiation dose delivered to the patient increases. Physical laboratory testing of DBT radiation dose (ST mode, N-dose) for a standard breast (42 mm, 50% fibroglandular tissue, 50% adipose tissue) for one view equals 1.2 mGy, and the dose for a standard breast, for one view FFDM is 0.75 mGy. (K133972).

An evaluation of the average glandular dose per view was performed using the 298 subject pivotal study case cohort. Results from this evaluation are provided below.

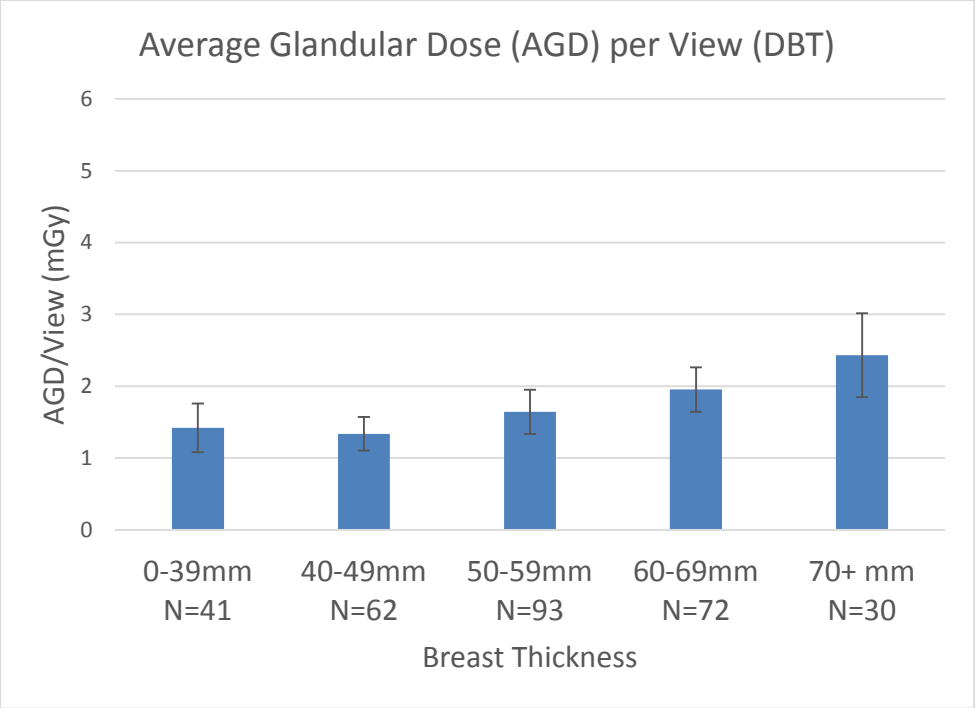


Figure 4. Average Glandular Dose, DBT only, per view, stratified by breast thickness, in the 298 patients enrolled in the pivotal MRMC study.

2. Effectiveness Results

The analysis of effectiveness was based on the 298 evaluable patients. The primary endpoint for the study was met. The pivotal study showed that radiologists had superior per-subject average area under the receiver operating characteristic (ROC) curve (AUC) for FFDM + DBT, 0.837, versus FFDM, 0.784. The increase in average AUC was 0.053 (two-sided 95% CI: 0.028, 0.078; $p < 0.01$). Analysis of alternative free-response operating characteristic (AFROC) curves which allow multiple reader findings per case, and worst-case analysis re-classifying some recall and negative cases without one-year negative follow-up as cancer cases, support the robustness of this conclusion.

The average empirical ROC plot across readers for FFDM + DBT is entirely above the average for FFDM (Figure 5).

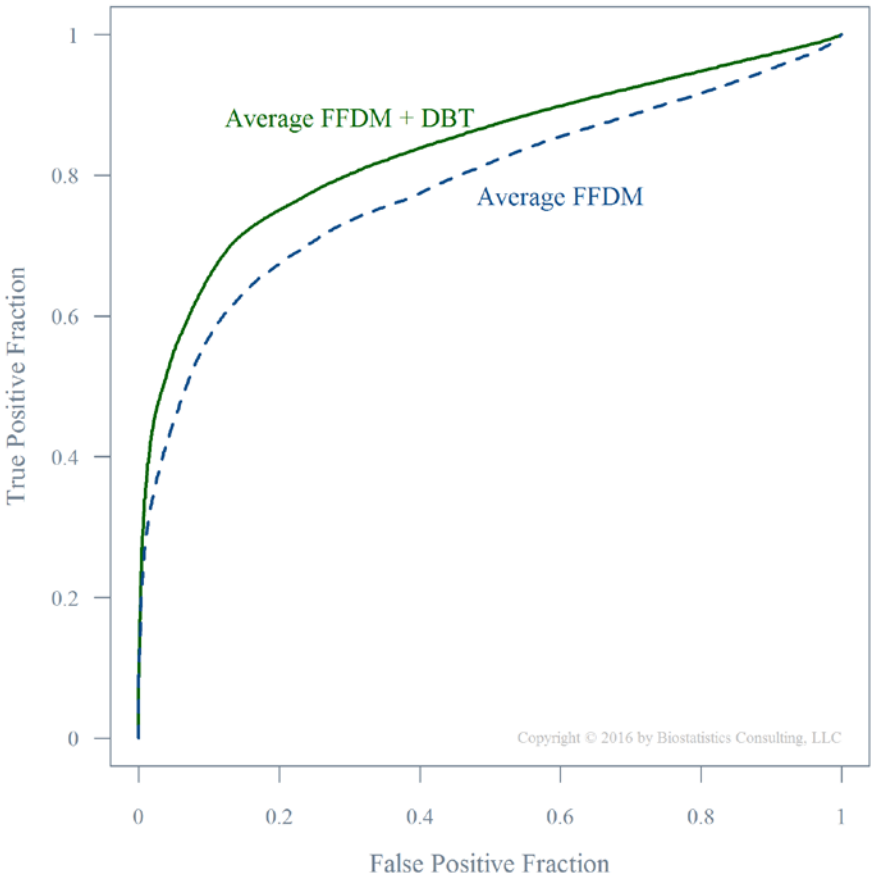


Figure 5. Average of Empirical ROC Plots for FFDM and FFDM + DBT.

Supportive analysis: JAFROC. Alternative free-response receiver operating characteristic (AFROC) curves, which allow multiple reader findings per case, were used in supportive analysis of the primary aim (Figure 6).[6] Radiologists had superior AFROC figures of merit (FOMs) for FFDM + DBT, 0.813, versus FFDM, 0.763. The increase in average FOM was 0.050. Therefore, the results for the primary endpoint can be considered to be robust to deriving, from one or more reader findings, a single score per case requiring correct lesion localization.

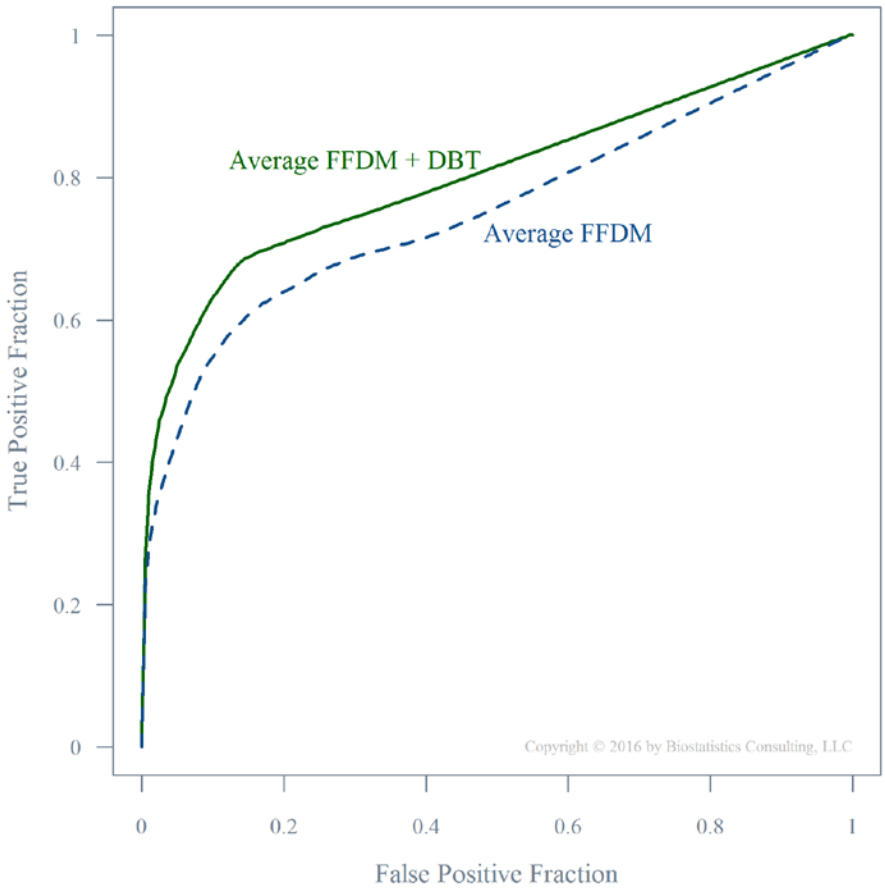


Figure 6. Average of Empirical AFROC Plots for FFDM and FFDM + DBT.

Supportive analysis: Missing one-year follow-up. Primary analysis of AUC classified recall and negative cases without one-year negative follow-up as non-cancer cases. A "worst case" AUC analysis was performed exploring robustness of the results to this classification decision. Using plausible cancer rates during follow-up we obtained 3 as the number of cases to be re-classified as cancer. The estimated increase in AUC for FFDM + DBT versus FFDM in the worst-case analysis was 0.049. We therefore consider the results of AUC analysis to be robust to classifying as non-cancer cases the 72 out of 190 recall and negative cases that are missing one-year negative follow-up

3. Secondary Endpoints

   The following preoperative characteristics were evaluated for potential association with outcomes: recall rate for non-cancer cases, sensitivity, recall rate for cancer cases, specificity.

   The study's type I error rate at alpha = 0.05 was controlled by performing hypothesis testing hierarchically in the pre-specified fixed sequence. Recall rate

for non-cancer cases (secondary endpoint 1): Radiologists had superior (lower) recall rate in non-cancer cases for FFDM + DBT, 0.262, versus FFDM, 0.362. The decrease in average recall rate was 0.100 (two-sided 95% CI: 0.066, 0.134; $p < 0.01$). Recall rate was analyzed using the yes or no answer to the separate Recall question.

Per-subject sensitivity (secondary endpoint 2): Radiologists had non-inferior per-subject sensitivity for FFDM + DBT versus FFDM. The increase in average per-subject sensitivity was 0.116 (two-sided 95% CI: 0.071, 0.161; non inferiority $p < 0.01$ for non-inferiority margin delta = 0.05). Analysis of sensitivity was based on forced BI-RADS scores requiring correct lesion localization, with BI-RADS 4 or 5 considered a positive test (true positive, TP).

Recall rate for cancer cases (secondary endpoint 3): Radiologists had non-inferior recall rate for cancer cases for FFDM + DBT, 0.771, versus for FFDM, 0.740. The increase in average recall rate for cancer cases was 0.031 (two-sided 95% CI: -0.004, 0.066; non-inferiority $p < 0.01$ for non-inferiority margin delta = 0.05). Recall rate was analyzed using the yes or no answer to the separate Recall question, requiring correct lesion localization in these cancer cases.

Per-subject specificity (secondary endpoint 4): Radiologists did not have high per-subject specificity. Analysis of specificity was based on forced BI-RADS scores, with BI-RADS 1, 2 or 3 considered a negative test (true negative, TN). Average specificity was less for FFDM+DBT compared to FFDM alone (0.878 for FFDM + DBT and 0.897 for FFDM; two-sided 95% CI of difference in specificity: -0.039, 0.001).

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

A. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical research studies included the following radiologists, for which none of the clinical investigators or radiologists had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

- image acquisition study
  - one primary investigator
  - Six principal investigators, and
  - 20 sub-investigators
- pilot studies: 16 radiologists

- pivotal study 28 radiologists
- one truthing radiologist
- one training radiologist

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiological Device Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The multiple-reader multiple-case (MRMC) study showed that when two-view DBT (MLO and CC), acquired with the ASPIRE Cristalle DBT option, is used as an adjunct to FFDM images reader performance on average increases 0.053 AUC ROC units with two-sided 95% CI: 0.028, 0.078; $p < 0.01$.

Combined with physical laboratory test results and sample image evaluation, the pivotal study results demonstrate that the ASPIRE Cristalle DBT option used as an adjunct is superior to FFDM alone.

B. Safety Conclusions

The risks of the device are based on physical laboratory testing as well as data collected in a clinical study conducted to support PMA approval as described above. The risk of direct harm to the patient is minimal. There was one adverse event during the collection study, but this event was not related to the proposed device.

The risk posed by the proposed device is similar to that of other screening and diagnostic mammography devices.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

The ASPIRE Cristalle DBT option is used to reconstruct the breast volume from limited angle projections while reducing the tissue overlapping effect observed in two-dimensional projections. It is likely to benefit a substantial number of screening patients whose cancers could have otherwise been missed due to tissue

superimposition (false negatives), or who may otherwise have been unnecessarily referred for additional workup (false positives).

The proposed device has no significant risk of direct harm to the patient.
The primary risk of the device comes from the possibility of false positive and false negative clinical decisions when using the images produced by the ASPIRE Cristalle DBT option. The applicant conducted an MRMC study to compare the performance of readers with FFDM alone and with FFDM plus two-view DBT. The study design is consistent with other mammography studies. Because MRMC studies are conducted outside some clinical norms (with an enriched case set, and without patient history), the generalizability of some figures of merit such as recall rate, sensitivity and specificity is limited. Nonetheless, the design is considered acceptable in order to reduce the size of the trial and avoid confounders.

Adding two-view DBT as an adjunct to FFDM requires additional exposure to ionizing radiation. Overall, the FFDM plus two-view DBT mammography exam remains a low dose examination. The risk associated with exposure to low dose radiation is theoretical and long-term, while an undetected breast cancer, particularly of the invasive type, is an immediate risk to a patient.

Additional factors to be considered in determining probable risks and benefits for the ASPIRE Cristalle DBT option included two study design choices that added some uncertainty to the estimated difference of reader performance between FFDM and FFDM plus two-view DBT. These were the method used to assign a POM score to a case by combining the lesion level scores and the classification of subjects without negative one-year follow-up as non-cancer. Supportive analyses indicate that the impact of these design choices is unlikely to be large enough to alter the study conclusions.

Patient Perspective:
This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information described above, the data support that the probable benefits of using the ASPIRE Cristalle DBT option as an adjunct to FFDM (in accordance with the indications for use) outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the ASPIRE Cristalle DBT option when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on January 10, 2017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.