Density MATTERs

(Molecular Breast Imaging (MBI) And Tomosynthesis To Eliminate the Reservoir)

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1. INTRODUCTION

1.1 Rationale for Proposed Study

Breast density has been found in multiple studies to be the primary factor in mammography failure and to increase the odds of missed breast cancer by nine- to fifteen-fold.[1-4] While mammography registry studies have reported sensitivities as high as 82% for women with dense breasts,[5] these studies inflate the sensitivity of mammography by failing to account for tumors that are occult both on the study mammogram and clinically during the study interval. In contrast, studies in which mammography is compared against a supplemental screening technique demonstrate that the sensitivity of mammography in women with dense breasts ranges from only 21% to 50%,[6-11] revealing that mammography misses over half of tumors in dense breasts. The average percent mammographic density decreases with increasing age, which explains why the limitations of mammography are more pronounced in younger women[12-14]: the rate of breast cancer not detected by screening mammography is 15 times as high in women 40 to 49 years of age with breasts that are in the most dense category (extremely dense) vs. the least dense category (almost entirely fatty).[4]

Breast density is also associated with advanced cancer presentation: in a cross-sectional analysis of tumor characteristics in 546 women diagnosed with invasive breast cancer, women with a tumor size >1.0 cm were more likely to have dense breasts compared with women with a tumor size ≤1.0 cm after adjusting for confounders.[15] Breast density is also the primary factor associated with the presentation of an interval cancer, defined as breast cancer diagnosed within 12 months of a negative screening mammogram[2]. The odds ratio for an interval cancer is 17.8 for women with mammograms defined as having ≥75% density compared to those with <10% density.[12] When characteristics of interval cancers are compared in women with dense breasts (defined as ≥25% density) vs. those with < 25% density, tumors in dense breasts were more likely to be larger ($P < 0.001$) and have lymph node metastases ($P = 0.001$). However, there were no differences in proliferation rates between interval and screen-detected cancers in dense breasts, suggesting that interval-detected cancers in women with dense breasts are larger not because they are more biologically aggressive, but because of a delay in detection. The hazard ratio for breast-cancer specific mortality was three times higher for interval cancers compared to screen-detected cancers, but this association disappeared in the dense breast group after adjusting for tumor size.[16] This evidence suggests that detecting tumors at a smaller size in women with dense breasts would have a significant mortality benefit.

Breast density legislation has provided an important mechanism of informing women about the implications of breast density in masking cancers on mammography. Most state-mandated breast density letters contain language encouraging women to “use this information to discuss with your health care provider whether other supplemental tests in addition to your mammogram may be

appropriate for you" (Michigan letter). However, the recent update to the United States Preventive Service Task Force guidelines on breast cancer screening failed to provide guidance in making these decisions, stating that "Overall, many important questions remain about the potential role of breast density in individualizing screening approaches, and the current evidence is insufficient to recommend a specific screening strategy for women with increased breast density"[17]. According to a recent national survey conducted by our team, almost half of screening-eligible women report that receipt of information about breast density without guidance on decision making would cause anxiety and confusion, [18] underscoring the need for data about relative benefits and harms for the supplemental screening options to inform women and providers.

1.2 Gaps in Evidence for Supplemental Screening

Current evidence for supplemental screening is insufficient for several reasons. First, previous trials have compared supplemental screening options to 2D mammography: now that digital breast tomosynthesis (DBT) is rapidly becoming the standard screening approach, it is important to reassess supplemental screening performance relative to DBT. Second, whole breast ultrasound (WBUS) is becoming the default option for supplemental screening due to its widespread availability and the perception of no risk due to lack of ionizing radiation. However, the limitations of WBUS include a very high false positive rate (>25% reported in some studies) and a modest incremental cancer detection rate (ICDR) of 2 to 4/1000 when compared with a functional supplemental screening test such as MRI.[8,19,20] Adopting a supplemental anatomic imaging technique, such as ultrasound, to compensate for the limitations of the standard anatomic screening technique, which is soon to be DBT, fails to harness the advantages conferred by a functional imaging technique.

1.3 MRI as a Supplemental Screening Tool

MRI, unlike mammography and ultrasound, is a functional breast imaging tool and has consistently demonstrated the highest yield of cancer detection of any breast imaging modality (Incremental cancer detection rate [ICDR] after negative mammography and WBUS was 14.7/1000 in a U.S. population at increased risk and 11/1000 in an average-risk European population).[8,21] In another European study, the interval cancer rate after MRI was 0%.[11] In a cohort of BRCA carriers, invasive tumor size at diagnosis averaged 0.9 cm in the MRI group (13% node positive), compared with 1.9 cm in the mammography-only group (40% node positive). In the same cohort, serial MRI screening over a mean of 3.2 years reduced the incidence of late-stage disease presentation, from 6.6% in controls to 1.9% in women screened with MRI.[22] These findings illustrate that MRI screening reduces the reservoir of advanced and interval cancers left behind by anatomic modalities.

However, multiple barriers exist to implementing MRI beyond the high-risk group. MRI costs up to ten times more than other breast imaging modalities. Technical expertise is required to produce high quality examinations just as advanced radiologist training is required for interpretation to

minimize variability in specificity.[23] It is not known whether these barriers can be overcome by abbreviated MRI, which uses a scan time of less than 10 minutes and thus could potentially reduce cost of the examination. Additional barriers include recall rates as high as 26% in some studies, [8] potential contra-indications, and concerns about intracranial gadolinium accumulation.[24-26] These barriers to MRI screening implementation beyond the high-risk group underscore the need to identify more cost effective functional imaging techniques with a lower rate of false positive findings.

1.4 Molecular Breast Imaging as Functional Screening Tool

Molecular Breast Imaging (MBI) is a nuclear medicine technique utilizing a specialized gamma camera optimized for imaging the breast. MBI and MRI are both functional imaging techniques: whereas MRI exploits different vascular properties of tumors relative to normal breast tissue, MBI exploits heightened mitochondrial activity, leading to preferential uptake of ^{99m}Tc-sestamibi in breast tumors, regardless of surrounding breast density. Unlike older-generation scintillating gamma cameras (e.g. scintimammography or breast-specific gamma imaging), MBI employs solid-state cadmium zinc telluride (CZT) detectors in a dual-head configuration, allowing for improved count sensitivity, spatial resolution, energy resolution, and lesion detection, along with an attendant reduction in radiation dose.[27,28]

In two prospective screening trials performed at Mayo Clinic Rochester by our team involving over 2500 asymptomatic women presenting for screening with dense breasts on previous mammogram, the addition of MBI to 2D digital mammography increased breast cancer detection almost four-fold.[9,10] In the most recent trial, the ICDR of MBI was 8.8 per 1000. The ICDR was significantly increased for invasive cancers but not DCIS, suggesting that MBI detects clinically important cancers rather than contributing further to overdiagnosis. The majority of cancers detected by MBI were node negative, confirming its role in early detection. MBI also detected node positive and large cancers that were mammographically occult, thus unveiling the reservoir of potentially lethal cancers left undetected by mammography. MBI also demonstrates favorable false positive and biopsy rates relative to screening WBUS and MRI. The addition of MBI to mammography raised the recall rate by 6.6%. MBI is FDA-approved, clinically available at over 50 U.S. sites to date, less expensive than mammography (at our institution), and much less complex to interpret relative to WBUS or MRI.

Efforts by our team over the past decade to improve detector technology and optimize injection and patient preparation procedures have resulted in a low-radiation dose MBI protocol. For the proposed study, 8 mCi (300 MBq) ^{99m}Tc-sestamibi will be used, delivering an effective radiation dose (a metric that considers burden and risk to the entire body) of 2.4 mSv. The dose of MBI combined with DBT (~0.5 mSv) would be 2.9 mSv. This total dose is considered safe for routine

screening use, as it is below the level of natural background radiation (3 to 10 mSv) and consistent with national and international guidelines stating that risks of medical imaging at doses below 50 mSv are "too low to be detectable and may be non-existent".[29-31] In addition, sestamibi is a commonly-used radiopharmaceutical with an excellent safety profile, with over 30 years of clinical use in cardiac and parathyroid testing.

1.5 Significance of the Study

The significance of this study is that it will be the first prospective trial to compare MBI, a relatively low-cost functional breast imaging technique, to DBT, the new standard anatomic breast cancer screening technique in women with dense breasts. This study is also the first to evaluate two consecutive annual MBI scans to assess change in advanced cancer presentation after introduction of a functional imaging technique. These data will inform individualized decisions on supplemental screening and determine if a functional technique that is relatively low in cost and complexity of interpretation can eliminate the reservoir of clinically important breast cancers that remain occult on anatomic techniques. This study will also provide exploratory data about the optimal frequency of repeat MBI.

2. STUDY OBJECTIVES

2.1 Primary Endpoint

The primary aim for this study is to compare the **rate of detection of invasive cancers** between DBT alone vs. the combination of DBT with supplemental MBI at Year 1 screening.

2.2 Secondary Endpoints

Secondary Endpoints include the following:

1. To compare the invasive cancer detection rates of DBT alone vs. MBI alone at Year 1 screening.
2. To compare the screening performance metrics of sensitivity, specificity, recall rate, biopsy rate, positive predictive value and negative predictive value for DBT and MBI.
3. To compare tumor characteristics of all cancers (invasive and noninvasive) detected on DBT and MBI, including size, nodal status, and molecular subtype.
4. To assess the reduction in advanced cancer rate with incorporation of MBI screening by comparing advanced cancer rate observed at Year 2 screening relative to that at Year 1.
5. To assess the rate of interval cancers with incorporation of MBI screening.
6. To examine the relative performance of DBT and MBI within subgroups categorized by breast cancer risk.

3. SELECTION OF PATIENTS

Potentially eligible patients who are scheduled for a screening DBT will be prescreened based on their breast density on most recent prior mammography examination. Potentially eligible patients

will be contacted by letter or telephone to assess eligibility and to offer enrollment if eligible. Study patients will be enrolled in this study for up to 30 months.

3.1 Inclusion Criteria

1. Patient is a consenting female age 40-75 years.
2. Patient is scheduled for routine screening DBT.
3. Patient is asymptomatic for breast disease.
4. Patient had heterogeneously dense or extremely dense breasts on most recent prior mammography examination (BI-RADS c or d) within 24 months of enrollment.
5. Patient is able to participate fully in all aspects of the study (completing study visits and study data collection).
6. Patient understands and signs the study informed consent.
7. Patient anticipates being able to return one year after study enrollment to complete the second round of screening.

3.2 Exclusion criteria

1. Patient is currently pregnant or plans to become pregnant during the course of the study.
2. Patient is currently lactating.
3. Patient has had a prior MBI.
4. Patient has had a prior whole breast ultrasound (WBUS) for screening, with either a hand-held ultrasound probe or automated system, within 12 months prior to study enrollment.
5. Patient has had a prior breast MRI.
6. Patient has had a prior contrast-enhanced mammogram (CESM or CEDM).
7. Patient is concurrently participating in any other breast imaging research studies that involve undergoing additional breast imaging tests beyond routine screening with mammography, including but not limited to contrast-enhanced mammography, WBUS, MBI, or contrast-enhanced breast MRI.
8. Patient has had a breast biopsy within 3 months prior to study enrollment.
9. Patient has had breast surgery within 12 months prior to study enrollment.
10. Patient is currently undergoing treatment for breast cancer or planning surgery for a high-risk breast lesion (ADH, ALH, LCIS, papilloma, radial scar).
11. Patient is currently taking a chemoprevention agent for breast cancer risk reduction or osteoporosis prevention (tamoxifen, raloxifene, anastrazole, letrozole, exemestane).
12. Patient has a known history of any condition or factor judged by the investigator to preclude participation in the study or which might hinder study adherence.

4. STUDY DESIGN

A total of 3006 participants will be enrolled in this study across multiple sites. This study will directly compare the results from two clinical procedures, Digital Breast Tomosynthesis (DBT) and Molecular Breast Imaging (MBI). After enrollment, study participation involves 2 study visits for breast screening – one at the beginning of the study and a second visit one year later. Participants will be enrolled in the study for up to 2.5 years (30 months) to ascertain breast cancer status, and may be contacted at the end of study if breast cancer status cannot be ascertained based on chart review, alone. Study schema is provided in Figure 1 and study schedule in Table 1.

Figure 1: Study Schema

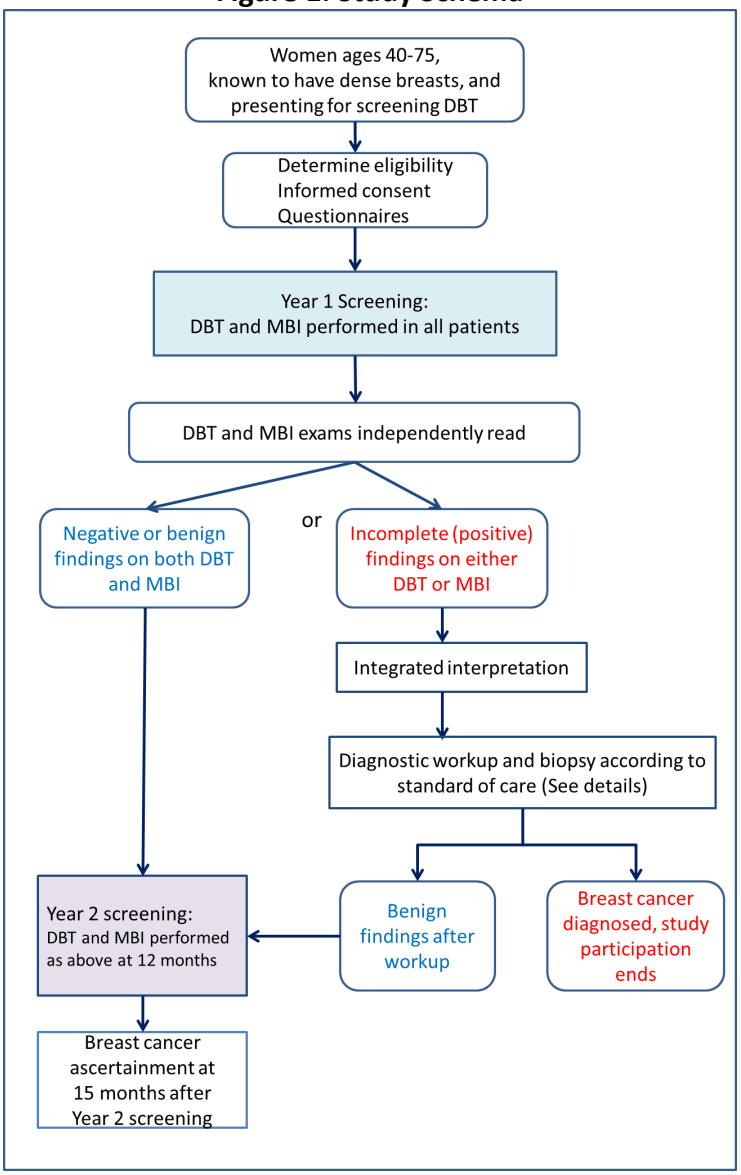

Table 1: Study Schedule

	Pre-Screening	Enrollment	Study Visit 1[1,2]	Study Visit 2[2]
Telephone Prescreen Eligibility	X			
Inclusion/Exclusion Criteria		X		
Informed Consent		X		
Medications		X		X
Demographics		X		
Breast Health History and Risk Assessment Survey[4]		X		
Abbreviated Breast Health History and Risk Assessment Survey[4]				X
Urine Pregnancy Test (if necessary)			X	X
DBT and MBI Exams[3]			X	X[5]

[1]Enrollment and study visit can be completed in one visit or over the course of two visits.
[2]Study Visits can be completed within 3 business days.
[3]DBT and MBI exams are targeted to be performed on the same day if possible and required to be completed within three business days of each other prior to initiation of any diagnostic workup.
[4]In order to minimize the amount of time participants will spend at this visit; they will be given the option of having the breast health history and risk assessment survey e-mailed to them. It participants choose this option; they will need to have this survey completed and submitted prior to study visit 1. If not, they will be asked to complete the survey while in-person prior to their radiology imaging.
[5]Should be targeted for 335 to 455 days from Year 1 MBI screening.

5. IMAGING

5.1 Imaging Procedures

At Year 1 screening, all patients will undergo both DBT and MBI targeted to be performed on the same day if possible and required to be completed within three business days of each other prior to initiation of any diagnostic workup. All patients who did not receive a diagnosis of breast cancer during Year 1 will undergo subsequent annual MBI targeted to be performed at approximately one year (Year 2 screening) after Year 1 screening; and should be targeted for 335 to 455 days from Year 1 MBI screening. The Year 2 MBI should be scheduled within 3 business days of the Year 2 DBT if possible; completion of Year 2 DBT is encouraged but not required.

5.1.1 DBT Procedure

DBT technique will be defined as per standard of care, which may include CC and MLO tomosynthesis views with either a 2D full field digital mammogram or synthetic 2D views.

5.1.2 MBI Procedure

1. Equipment – MBI examinations will be performed on FDA-approved direct conversion dual-head cadmium zinc telluride gamma camera systems (Discovery NM 750b, GE Healthcare, or LumaGem, CMR Naviscan).

2. Technologist – Nuclear medicine technologists will perform radiotracer injections.

3. Patient preparation – Patients will be asked to fast for a minimum of 3 hours prior to the MBI examination, when possible, as prior studies have shown fasting to improve uptake of Tc-99m sestamibi in breast tissue by reducing splanchnic and hepatic blood flow.[32] Patients may take fluids, including black coffee, tea, diet soda and water. Patients will remove all clothing and jewelry above the waist and put on a patient gown. Patients may be given a warm blanket to wrap around their shoulders and chest for approximately 15 minutes prior to the Tc-99m sestamibi injection, in order to increase peripheral blood flow to breast tissue and thus improve Tc-99m sestamibi uptake.

4. Tc-99m sestamibi injection – The technologist should verify that the patient is not pregnant or breast feeding prior to injection of Tc-99m sestamibi. A Nuclear Medicine technologist will deliver an intravenous injection of the Tc-99m sestamibi dose in an antecubital vein of either arm. The target administered activity will be 8 mCi (300 MBq) Tc-99m sestamibi. Residual activity after injection should be measured and decay-corrected to calculate the actual administered activity for each MBI examination. The requested dispensed activity of Tc-99m sestamibi to achieve an approximate administered activity of 8 mCi will depend on site-specific standard of care. Infiltration or extravasation of the injected dose into the soft tissue rarely occurs (~1-2% of studies). If infiltration is suspected, the technologist will observe the count rate obtained on a persistence view prior to beginning imaging. If the count rate is lower than typical (defined as less than 0.2 kcts/minute in the CC view and less than 0.3 kCts/minute in the MLO view for an average-sized breast) the technologist will image the injection site to evaluate. If there is no evidence of infiltration on imaging of the injection site, the technologist will proceed with the breast images. If infiltration is confirmed by both low count rates and high uptake at the injection site, the technologist will ask for the patient's consent to proceed with a second injection of 8 mCi Tc-99m sestamibi. The patient will be given the option to refuse a second dose and continue with the study, although poor image quality may be obtained, or to discontinue MBI imaging and thus end study participation.

5. Image Acquisition - MBI imaging will commence immediately after injection. Two views of each breast will be acquired in the cranio-caudal and mediolateral oblique projections.

Acquisition duration will be 10 minutes per view. Images will be acquired using an energy acceptance window of 110-154 keV. For each view, patients will be seated with the breast positioned between the two detectors. The persistence-scope should be used to validate correct breast positioning. If available, the recent mammogram can be viewed to replicate positioning on the MBI. Light compression is applied to stabilize the breast and to limit motion artifact. Placement of pillows behind the patient's back is recommended to reduce motion and increase comfort. Verification of the patient's comfort level and ability to complete 10 minutes of imaging in the position should be done before acquisition begins. Compression thickness for each MBI view will be recorded. In participants with breasts larger than the detector field of view, the technologist may opt to acquire two 10-minute tiled MLO views of each breast, in place of a CC and MLO view, in order to ensure that the entire breast is included in the image set. During the acquisition of each view, the technologist will briefly place the appropriate Co-57 laterality markers (R for right and L for left) in the field of view until well seen on the persistence screen. The patient will be visually monitored by the nuclear medicine technologist from the time of injection of the radionuclide until image acquisition is completed.

6. Post-acquisition processing – Following completion of the acquisition, the technologist will format the acquired images in the standard format used for MBI display and interpretation, showing 8 images collected from bilateral CC and MLO positions from each of two detector heads.

5.2 Imaging Interpretation

DBT and MBI screening studies will be interpreted by two different radiologists, each blinded to the other modality. The interpreting radiologist may refer to any other breast imaging and breast clinical information from previous years while interpreting the DBT or MBI. At both Year 1 and Year 2 screening, the radiologist will only be blinded to results and images from the other screening test (DBT or MBI) performed within 3 business days as part of the study protocol. Interpretations will be recorded independently for both DBT and MBI. Following independent interpretation, if either exam received a positive interpretation, then the breast radiologist who interpreted the MBI will perform an integrated assessment.

5.2.1 DBT Interpretation

DBT interpretation will be performed during the course of routine clinical practice by radiologists using the standard of care American College of Radiology BI-RADS lexicon.[33] For the initial screen, BI-RADS categories of 0 (incomplete), 1 (negative), or 2 (benign) will be assigned. Interpretive findings, including lesion type, size, and location will be abstracted from the clinical

DBT report by study staff. A study radiologist will review the DBT exams with BI-RADS assessment 0 and assign a lesion ID and per-lesion assessment category for each lesion identified on the clinical DBT screening report. Categories 3, 4, and 5 are considered test positive.

5.2.2 MBI interpretation

MBI exams will be interpreted by study radiologists who have interpreted at least 50 MBI exams and/or have completed the American College of Radiology web-based training module. Study radiologists are required to pass an MBI interpretation quiz prior to interpreting study MBI examinations. MBI examinations will be assessed according to the established MBI lexicon[34] with assessment codes as follows: category 1, negative; category 2, benign; category 3, probably benign; category 4, suspicious for malignancy; category 5, highly suggestive of malignancy. A per-lesion assessment category will be assigned. Categories 3, 4, and 5 are considered test positive.

5.3 Diagnostic Workup of Screening Findings

Any diagnostic work-up imaging recommended from either screening study (DBT or MBI) will be postponed until completion of both blinded imaging study interpretations. If additional imaging is recommended on the basis of either DBT or MBI, an integrated interpretation will dictate further diagnostic evaluation.

Workup of DBT findings should be performed according to standard of care. MBI findings are allowed to generate additional diagnostic workup in the setting of a negative or benign assessment on DBT screening. However, a negative or benign assessment on MBI screening should not change recommendations generated by test-positive DBT.

The recommended diagnostic workup for DBT and MBI findings is detailed in Figures 2 and 3. For test-positive DBT findings, diagnostic mammography and/or targeted ultrasound will be performed as appropriate (Figure 2).

For test-positive MBI findings in the setting of a test-negative DBT screen, workup may include diagnostic mammographic views and/or targeted ultrasound and/or diagnostic MRI, as appropriate (Figure 3). If no suspicious correlate is seen on diagnostic mammogram or ultrasound for a lesion with assessment category 3 on MBI, a 6 month follow-up MBI is recommended. Lesions seen on MBI with assessment category 4 or 5, in the absence of a mammographic or sonographic correlate accounting for the MBI finding, would prompt a breast MRI.

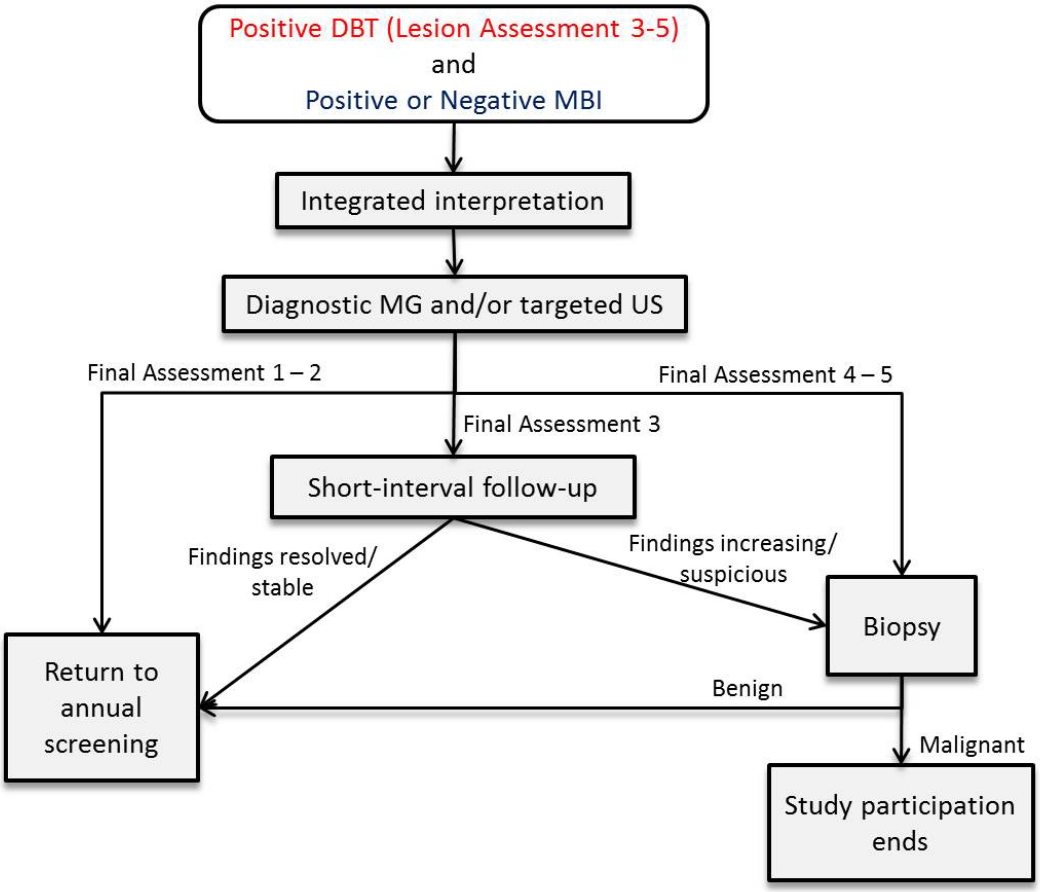

Figure 2: Diagnostic workup for lesions with positive DBT (assessment 3, 4, or 5) and any MBI assessment at initial screening. MG = mammogram; US = ultrasound

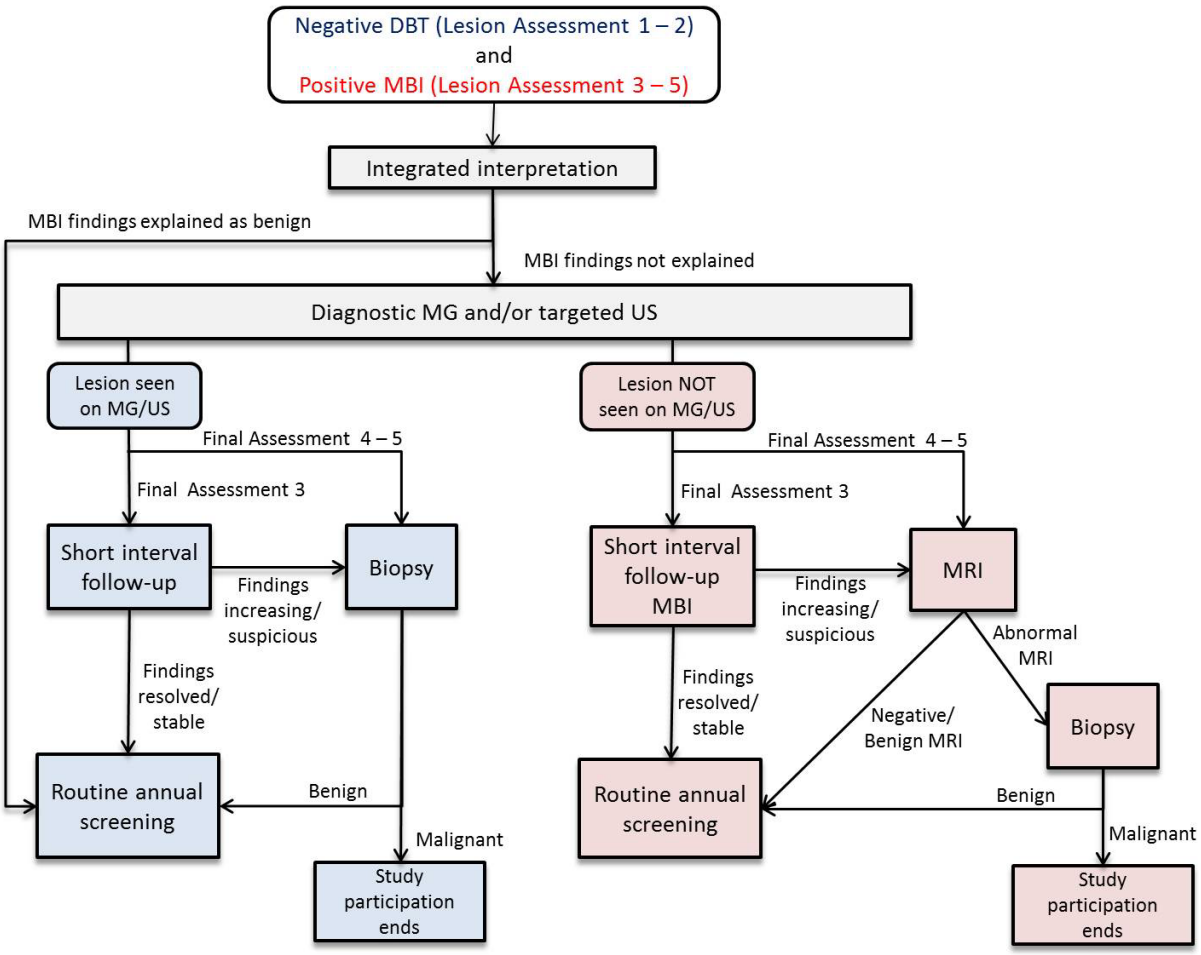

Figure 3: Diagnostic workup for lesions with negative DBT (assessment 1 or 2) and positive MBI (assessment 3, 4, or 5) at initial screening. MG = mammogram; US = ultrasound

6. ADVERSE EVENT REPORTING

An adverse event (AE) is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

As per NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 toxicity is defined as adverse events that are classified as either "possibly," "probably," or "definitely related" to the study .[35] The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study assignment in the event of an actual relationship developing. Adverse events and toxicities will be evaluated using all patients who have undergone any study imaging; summaries of those who have been included in the efficacy analyses will also be provided.

All adverse events will be reviewed that are presented through study staff's EPIC in-basket or Electronic Medical Record. Only those events that are determined by the Principal Investigator to be related to any aspect of the research will be documented and reported. Events that are not attributed will not be included in the study data and reported. However, all subjects will be asked to continue to report any adverse events.

A serious adverse event (SAE) is generally defined as any untoward medical occurrence that:

1. results in death
2. is life threatening
3. requires inpatient hospitalization or prolongation of existing hospitalization
4. results in persistent or significant disability/incapacity
5. results in a congenital anomaly.

All study subjects will be given a wallet card with the study team contact information 24/7. They will be educated on contacting the study team if any of these events occur. This will allow the study staff to be contacted if a serious adverse event occurs between study visits (up to 365 day time span).

7. DURATION OF FOLLOW-UP

Study participation involves 2 study visits for breast screening – one at the beginning of the study and a second visit one year later. Participants will be enrolled in the study for approximately 2.5 years (30 months) to ascertain breast cancer status, and may be contacted at the end of study if breast cancer status cannot be ascertained based on chart review, alone. If only one of the baseline

imaging tests (DBT or MBI) is completed, the patient will be excluded from the study and no data will be collected. Participant's breast cancer status will be obtained from chart review or patient contact targeted for 365 days after each screening year, but may be obtained from 335 days to 455 days after screening, unless the patient specifically requests to withdraw from the study. If a patient is diagnosed with a primary breast cancer during the study period, no subsequent follow-up or further study imaging will be required for this research study.

8. STATISTICAL CONSIDERATIONS

8.1 Study Design

This study employs a paired design in which all participants will undergo both DBT and MBI for two rounds of annual screening, defined as Year 1 and Year 2. Unless otherwise specified, the primary unit of analysis will be the patient.

8.2 Reference Standard

A study participant can be classified as having either positive or negative breast cancer status in a given screening year.

8.1.2 Establishing Year 1 Reference Standard

Positive Breast Cancer Status for Screening Year 1 is established if one of the following is true:

- A participant has a histopathologic diagnosis of breast cancer[a] within the time period from Year 1 screening[b] until Year 2 screening[c], not including Year 2 screening
- A participant does not undergo Year 2 screening[c] but has a histopathologic diagnosis of breast cancer[a] within 365 days of Year 1 screening.

Negative Breast Cancer Status for Screening Year 1 is established by any of the following, in order of best to least reliable determination:

1. A participant has both Year 2 screening MBI and DBT, both with negative or benign findings, or positive findings that are ultimately determined to be benign after diagnostic imaging workup or tissue diagnosis.
2. A participant does not complete both Year 2 screening MBI and DBT, but is followed through chart review or patient contact, resulting in documentation of any breast imaging test performed at least 335 days after Year 1 screening, with negative or benign findings, or positive findings that are ultimately determined to be benign after diagnostic imaging workup or tissue diagnosis.
3. A participant does not undergo Year 2 screening but is contacted at least 335 days after Year 1 screening and the participant herself confirms that she did not have a breast cancer diagnosed that meets the Positive Breast Cancer Status definition.
4. A participant does not undergo Year 2 screening but is followed through chart review at least 335 days after Year 1 screening and no breast cancer is reported to meet the Positive Breast Cancer Status definition.

A participant with breast cancer detected on Year 2 screening is assumed to have negative breast cancer status for Year 1 and the cancer diagnosis is included in the Year 2 analysis, not the Year 1 analysis.

8.2.2 Establishing Year 2 Reference Standard

Positive Breast Cancer Status for Screening Year 2 is established if one of the following is true:

- A participant has a histopathologic diagnosis of breast cancer[a] within the time period from Year 2 screening until the next annual screen (Year 2), not including the next annual screen.
- A participant does not undergo Year 2 screening[d] but has a histopathologic diagnosis of breast cancer within 365 days of Year 2 screening.

Negative Breast Cancer Status for Screening Year 2 is established by any of the following, in order of best to least reliable determination:

1. A participant is followed through chart review or patient contact, resulting in documentation of any breast imaging test performed at least 335 days after Year 2 screening, with negative or benign findings, or positive findings that are ultimately determined to be benign after diagnostic imaging workup or tissue diagnosis.
2. A participant does not undergo Year 2 screening[d] but is contacted at least 335 days after Year 2 screening and the participant herself confirms that she did not have a breast cancer diagnosed that meets the Positive Breast Cancer Status definition.
3. A participant does not undergo Year 2 screening[d] but is followed through chart review at least 335 days after Year 2 screening and no breast cancer is reported to meet the Positive Breast Cancer Status definition.

A participant with breast cancer detected on Year 2 screening is assumed to have negative breast cancer status for Year 2.

8.1.3 Participants Not Meeting Reference Standard Definitions

If a participant does not meet either definition for Positive or Negative Breast Cancer Status in a given screening year, for instance a participant who has no known breast cancer diagnosis but has no information available via chart review and cannot be contacted, will be considered “lost to follow up” and assumed to not have breast cancer in the analysis. In the event of a participant’s death, the date of death and cause of death will be recorded to determine if breast cancer was diagnosed and the length of follow up.

[a]The date of histopathologic breast cancer diagnosis is defined as the date on which tissue was obtained via biopsy or surgical excision, and subsequently determined to include invasive cancer (with or without DCIS) or DCIS.
[b]Year 1 screening is defined as having both Year 1 MBI and Year 1 DBT. If not performed on the same day, the date of Year 1 screening is the day Year 1 MBI is performed.

[c]Year 2 screening is targeted to be performed with both MBI and DBT approximately 365 days (target range 335 – 455 days) after Year 1 screening MBI. For purposes of establishing breast cancer status of Screening Year 1, Year 2 screening may be performed with any combination of breast imaging tests, most often including MBI, DBT, or both, but may also include breast MRI, WBUS, or CEDM; testing may be performed for either screening or diagnostic indications. The date of Year 2 screening used for reference standard is the earliest of these tests performed at least 335 days after Y0 screening.

[d]Year 2 screening is not conducted as part of the research study, but considered for purposes of establishing Year 2 breast cancer status as any documentation of breast imaging (MBI, DBT, MRI, WBUS, or CEDM) performed within 335 – 455 days after Year 2 screening.

8.3 Definitions of Screening Test Results

The result of either screening exam (DBT or MBI) on a patient with no cancerous lesions can be either true negative (TN) or false positive (FP). The per-patient score will be defined as the higher score between the two breasts or, if there are multiple scored findings within a breast, the maximum score within the patient.

1. A TN test result will be defined as a negative test score on a patient with a negative reference standard. For DBT, a negative BI-RADS score will be 1 or 2; a negative test score on MBI will be a score of 1 or 2 on the 5-point assessment scale.
2. A FP test result will be defined as a positive test score on a patient with a negative reference standard (BI-RADS 0, or BI-RADS 3 or higher for DBT; 3 or higher on the MBI assessment scale).

The result of either exam on a patient with at least one cancer can be either true positive (TP) or false negative (FN).

1. A TP test result will be defined as a positive test score and correct localization of the lesion on a patient with a positive reference standard.
    a. Correct localization will be determined by an expert radiologist reconciler as follows: A DBT or MBI finding will be deemed to correspond with a cancer (invasive or DCIS) if it is located in the same quadrant of the breast and at the same depth (anterior, middle, or posterior, if recorded on the pathology report).
    b. Any cancer found by pathologic analysis that does not have a matching DBT or MBI finding will be considered occult (false-negative) on that modality.
    c. Any DBT or MBI finding that does not match with a cancer on the pathology report will be considered in the analysis as a false-positive.
    d. Two or more discrete cancerous lesions identified on pathology may be deemed to match a single DBT or MBI finding if the lesions correspond in location with a larger imaging finding (e.g., the pathology report describes several small adjacent masses in a single quadrant, where on imaging, a single larger region in that quadrant is

described). The decision of whether several invasive foci match a single MBI finding (assuming the location matches) will be validated primarily by visual qualitative or morphologic assessment. For cases in which it is not clear qualitatively whether all foci can be accounted for by the one DBT or MBI finding, the imaging finding must be within 1 cm of the combined size of the invasive foci for them all to be included. If all invasive foci in a single quadrant cannot be accounted for by a single imaging finding, it will be assumed that the larger focus matches the imaging finding and the smaller focus or foci are occult.

e. In patients with core biopsy-proven cancer who undergo neoadjuvant chemotherapy before definitive surgery, an imaging finding may be deemed true-positive even if surgical pathologic findings are negative, as long as the finding corresponds with the quadrant and depth of the pre-therapy positive core biopsy (validated by review of postclip films or conventional imaging of the core biopsy). Cancerous lesions found on surgical pathologic examination after chemotherapy that do not have a matching DBT or MBI finding will be considered occult on the respective modality.

2. A FN test result will be defined as either a negative test score or a positive test score but not in the correct location on a patient with a positive reference standard.

8.4 Definition of Analysis Set

The Analysis Set for each screening year will be defined as the subset of enrolled patients who met eligibility criteria and completed screening imaging with both DBT and MBI.

8.5 Primary Endpoint

The primary aim for this study is to compare the rate of detection of invasive cancers between DBT alone vs. the combination of DBT with supplemental MBI at Year 1 screening.

For each modality, the detection rate of invasive cancers will be estimated as the proportion of participants in the analysis set who had an invasive cancer detected by the modality and verified by pathology. Because of the paired design and nature of comparing single modality alone vs combined modality screening results, the null hypothesis of equal detection rates is on the boundary of the support and assumptions of a standard 2-sided McNemar's test are violated. The hypothesis will alternatively consider superiority by a margin using an exact binomial test. The margin will be defined such that the increase in rate of detection must be higher than 1 per 1000 (i.e., 0.1%).

8.6 Secondary Endpoints

1. **To compare the rate of detection of invasive cancers between DBT alone vs. MBI alone at Year 1 screening.**

The comparison will be based on a 2-sided McNemar's test at statistical significance level alpha= 0.05.

2. **To compare the screening performance metrics of sensitivity, specificity, recall rate, biopsy rate, positive predictive value and negative predictive value for DBT and MBI.**
   For both years of the study imaging (Year 1 and Year 2), the following secondary endpoints will be analyzed to compare performance of
   - DBT alone vs. MBI alone, and
   - DBT alone vs. the combination of DBT with supplemental MBI.

   Sensitivity will be estimated for each modality as the proportion of women with breast cancer who have true positive test results. **Specificity** will be estimated as the proportion of women without breast cancer who have TN test results. Uncertainty in the estimate of sensitivity will be quantified through a two-sided 95% confidence interval (CI) based on the binomial distribution. If a sufficient number of radiologists interpret exams from multiple patients with breast cancer, secondary analysis may also include a 95% CI and chi-squared test adjusted for clustering of results within radiologist to allow generalization to both the population of patients and the population of radiologists.[36] For comparisons of DBT alone vs. the combination of DBT with supplemental MBI, a structural zero results due to the paired nature of the data and direct comparisons cannot be tested under a null hypothesis of equivalence. Analysis will alternatively focus on the conditional diagnostic odds ratio (cDOR) to quantify the added value of MBI over DBT alone.

   Recall rate (defined as the proportion of patients recalled from the screening test for diagnostic workup among the total number of patients screened), and **biopsy rate** (defined as the proportion of patients in whom biopsy is generated from a particular modality among the total number of patients screened) will be estimated employing analytical strategies similar to sensitivity and specificity. McNemar's test will be used to compare rates between two modalities.

   Predictive values will be estimated for each modality based on data pooled across radiologists. PPV1 (the proportion of patients with breast cancer among patients with abnormal screening examinations), PPV3 (the proportion of breast cancers diagnosed among biopsies performed), and NPV (the proportion of patients without breast cancer among those with normal screening examinations) will be determined. The primary unit of analysis will be the patient, expect for PPV3, in which the primary unit of analysis will be the biopsied lesion. The method of Moskowitz and Pepe will be used to compare relative

predictive values between the two imaging modalities.[37] Secondary analyses may adjust for clustering of results within radiologist.

3. **To compare tumor characteristics of all cancers (invasive and noninvasive) detected on DBT and MBI, including size, nodal status, and molecular subtype.**
   The analysis comparing tumor characteristics will be descriptive. Size, nodal status, and molecular subtype (including estrogen and progesterone receptor status, HER-2 status, Ki-67 and Oncotype DX score as available) will be abstracted from clinical final pathology reports from all biopsies and surgeries performed. The distribution of sizes will be summarized by ordinary numeric (e.g., means, SDs, range) and graphical (e.g., histograms, density smoothers) summaries. Descriptive summaries of the lesions identified with MBI but not DBT and vice versa will also be calculated to understand the differences in performance should one be identified.

4. **To assess the reduction in advanced cancer rate with incorporation of MBI screening by comparing advanced cancer rate observed at Year 2 screening relative to that at Year 1.**
   For the purpose of our analysis, advanced cancers are defined as cancers greater than 2 cm in maximum dimension (determined by measurements on pathology or imaging) and/or cancers that are lymph node positive, as these patients may be considered for neoadjuvant chemotherapy. To assess whether the incorporation of MBI screening reduces **advanced cancer rate,** the rate of advanced cancers detected at Year 2 screening will be compared to the rate at Year 1 screening. The rates of advanced cancers, together with their respective 95% confidence intervals, will be estimated for Year 1 and Year 2. Comparison in the rates between Year 1 and Year 2 will utilize the test of two proportions based on exact binomial distributions.

5. **To assess the rate of interval cancers with incorporation of MBI screening.**
   For the purpose of our analysis, interval cancers are defined as cancers diagnosed not at study imaging but between Year 1 and Year 2 screening tests. The interval cancer rates per 1000 women screened will be determined as the proportion of participants in the analysis set who had an interval cancer diagnosed and verified by pathology. To assess whether the incorporation of MBI screening, with one year of follow-up for breast cancer results in a "low" interval cancer rate, we will compare the interval cancer rate found in our study to the reported interval cancer rates for a population of women with dense breasts.
   Per Breast Cancer Surveillance Consortium (BCSC) analysis[38] the interval cancer rate among women with dense breasts was 89 per 100,000 women (or ~0.9 per 1000). The authors of this analysis considered an interval cancer rate greater than 1 case per 1000 mammography examination as an unacceptable performance level. We will estimate the rate of interval

cancers from our study and provide a 95% confidence interval. The performance level of this screening approach will be considered unacceptable if the lower bound of the confidence interval exceeds 1/1000 (i.e. 7 or more interval cancers in this cohort).

6. **To examine the relative performance of DBT and MBI within subgroups categorized by breast cancer risk.**
   The comprehensive risk factor collection planned in this study will allow accurate risk estimation promoting generalizability of results by type of risk model and level of risk. As an exploratory analysis, we will examine if the risk estimates determined with Gail, BCSC, Claus, and Tyrer-Cuzick models may predict a subgroup of women with MDB who are more likely to benefit from a specific supplemental screening. In particular, the relative performance of the screening modalities (sensitivity and specificity) will be characterized separately, within subgroups of patients defined by various levels of risk. The statistical power to discern differential performances of the screening modalities among different risk subgroups may be limited due to the restricted sample size in these subgroup analyses.

8.7 Sample size and power analysis

The sample size for this clinical trial was chosen to allow adequate power to detect difference in invasive cancer detection between DBT alone vs. the combination of DBT with supplemental MBI.

This is the first study to directly compare performance of DBT and MBI. Our choice of plausible values for the incremental detection of invasive cancers anticipated for MBI at Year 1 imaging, relative to DBT, is based on a composite analysis of two studies, one comparing MBI to 2D digital mammography, and one comparing 2D digital mammography to DBT:

- In a previous comparison of MBI to 2D digital mammography in average-risk women with dense breasts, the invasive cancer detection rate was 1.9 (95% CI 0.6 to 5.6) for 2D mammography vs. 8.8 (95% CI 5.1 to 14.7) for 2D mammography plus MBI, giving an incremental cancer detection rate (ICDR) for invasive breast cancers of 6.9 per 1000.[10]
- In a comparison of 2D digital mammography and DBT in a general population screening program, the invasive cancer detection rate for women with dense breasts was 3.4 (95% CI 1.5 to 5.4) for 2D mammography vs. 4.7 (95% CI, 2.9 to 6.6) for DBT (p=0.4), allowing us to estimate that the ICDR of invasive breast cancers for DBT is 1.3 per 1000.[39]

Thus the expected difference in invasive cancer detection rate between DBT with supplemental MBI and DBT alone is 5.6 (=6.9 – 1.3). We conservatively estimated the difference in yield of invasive breast cancers between DBT with supplemental MBI and DBT alone to be approximately 5 per 1000. To allow for potential smaller effect size that may be observed in a multicenter setting,

as has been observed with other modalities, we chose to power the study to detect an effect size of 4 per 1000 additional invasive cancers detected with supplemental MBI.

We will test the hypothesis that DBT with supplemental MBI results in an incremental invasive cancer detection rate of more than 1 per 1000 screenings (0.1%) compared to that of DBT alone. Assuming the difference in invasive cancer detection rates is 0.004, a sample size of 2631 will be needed to achieve 90% power using a one-sided exact binomial test with significance level alpha = 0.025 (calculation based on PASS 15).

8.8 Considerations for Expected Attrition

To account for attrition due to incomplete follow-up leading to non-evaluability of the primary endpoints or inconclusive findings from either screening modality, we will plan to over accrue an additional 375 participants, which leads to a **total sample size of N = 3006**. A high rate of missing data is not anticipated. For baseline variables that have more than 10% data missing, the missingness pattern will be examined and when appropriate, missing data imputation techniques may be employed.

8.9 Interim Analysis

Since this is a paired comparative study comparing the diagnostic accuracy of two imaging modalities, no formal interim analysis regarding safety/efficacy/futility is planned.

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