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TITLE: Contrast Enhanced Spectral Mammography vs. MRI for Breast Cancer Screening

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SUMMARY OF CHANGES

For Protocol Amendment# to:

NCI Protocol #: *NI*A
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NCI Version Date:
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#	Section	Page(s)	Change
1.		1,2,3	!Staffing changes
2.		4,8,11,12	Scientific changes, decrease in prospective recruitment
3.			
4.			
5.			

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Study Exempt from IND Requirements per 21 CFR 312.2(b).

SCHEMA

Figure 1. Reader Study

Prospectively acquired imaging sets will be added to existing cases for the case collection. Types of cases and the number of cases to be recruited are presented. Cases to be used for the reader study are shaded green.

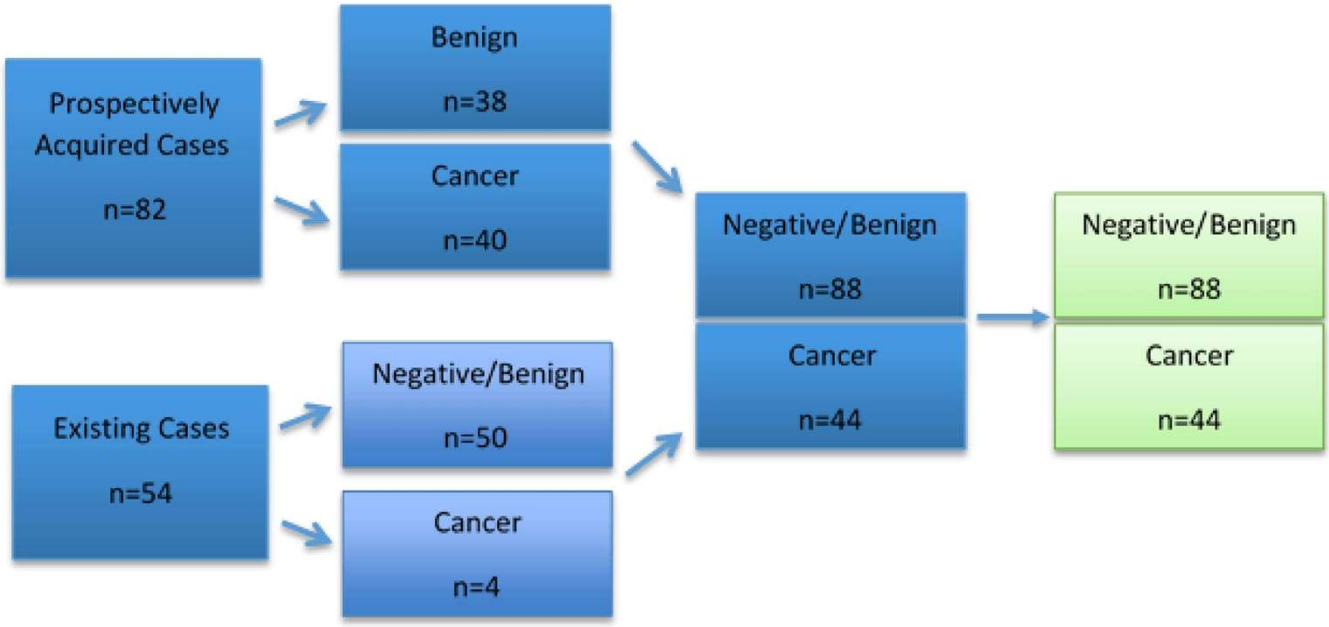
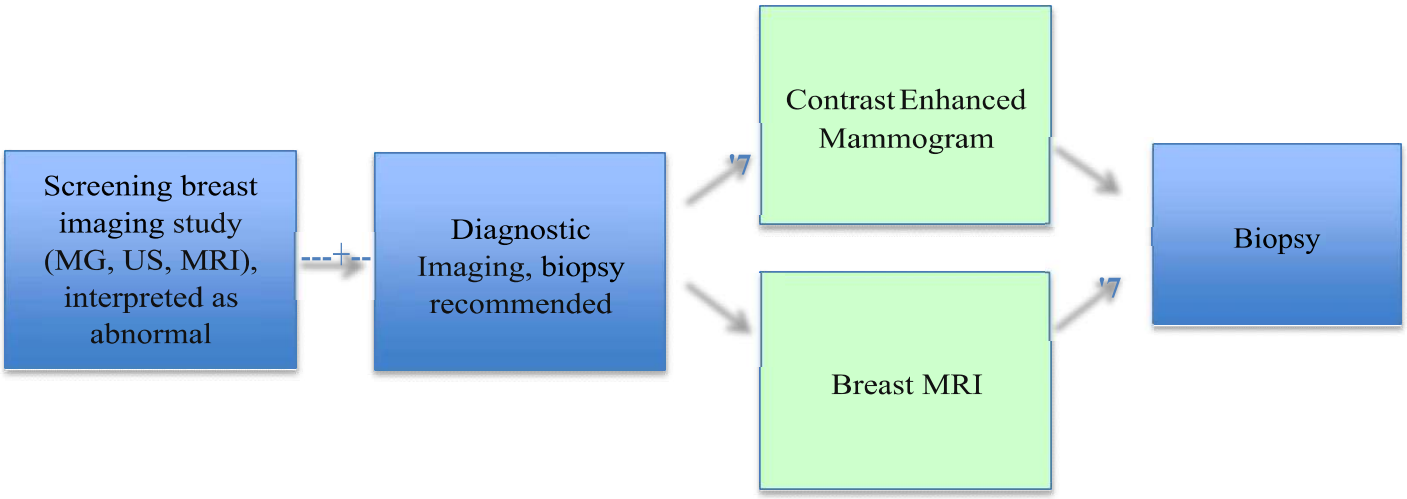


Figure 2. Prospective Case Collection

Additional images for the reader study will be prospectively recruited. These patients will be recruited prior to receiving breast biopsy (shaded green) based on a finding initially seen on screening mammography.



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1. OBJECTIVES

The objective of this study is to show the Contrast Enhanced Spectral Mammography (CESM) is non-inferior to breast MRI (complete and abbreviated protocols) for breast cancer screening.

1.1 Study Design

This study is a multi-reader, multi-case (MRMC) enriched reader study that will be performed over two years using imaging sets of CESM and breast MRI collected from a screening population.

1.1.1 Case Selection for the Reader Study

Cases to be included will be categorized as negative, biopsy proven benign, and biopsy proven malignant. The total number of cases required for each group can be seen in Figure 3.

Cases needed for reader study	**Total # of cases needed for reader study**
Negative/ Biopsy Proven Benign	88
Biopsy Proven Cancer	44
Total number of cases	**132**

Figure 3. Number of negative, biopsy proven benign, and biopsy proven cancer cases. Given the varying proportions identified in FDA approved studies and other MRMC imaging evaluations, this ratio of negative/biopsy proven benign to biopsy proven cancer cases was seen as acceptable. [1-5]

Of the 132 imaging sets required for the reader study, 54 were previously acquired through another research study (DF-HCC 14-225) and clinical practice. 4 of these cases were malignant. Cases acquired through DF-HCC 14-225 were incorporated into the Online Medical Record, as specified in the protocol, similar to those cases acquired for clinical practice. We are requesting a waiver of informed consent to include these imaging sets that are a part of the clinical record in the current reader study.

We will prospectively recruit the additional 40 cancers and 38 negative/benign cases necessary for the reader study. These cases will be prospectively recruited from a population of women who are undergoing biopsy in order to maximize the number of cancers identified. This will be discussed in more detail in Section 1.1.2.

Thus, the cases to be collected and used for the reader study will be broken down as demonstrated in Figure 1 of the Schema.

1.1.2 Prospective Image Acquisition:

CESM and MRI images will be prospectively collected to identify additional malignant and benign cases that are required for the reader study. All cases to be prospectively recruited will be selected from a population for whom a breast biopsy has been recommended based on an initial screening study, as illustrated in Figure 2. By performing the imaging prior to the biopsy, this ensures that there are no post-biopsy changes that may bias a radiologist reader during the reader study.

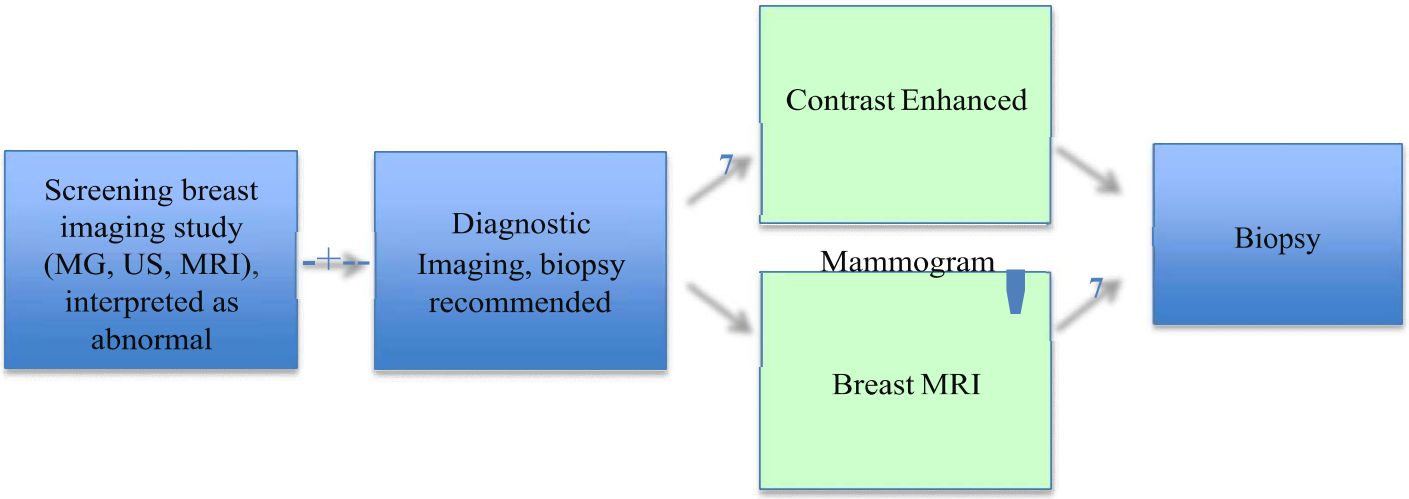

Figure 2. Additional images for the reader study will be prospectively recruited. These patients will be recruited prior to receiving breast biopsy (shaded green) based on a finding initially seen on screening mammography.

Screening and enrollment: Women will be identified at the time of their diagnostic work-up when a biopsy is recommended. If the participant meets screening requirements, informed consent will be obtained at that time and eligibility tests will be performed. Pregnancy tests will be checked on all premenopausal women and creatinine clearance (to evaluate renal function) will be checked according to the clinical protocol. If the participant meets all eligibility requirements, then she will be enrolled to the study.

To evaluate how CESM works with all types of cancer (both subtle and more obvious), patients will be recruited consecutively from BI-RADS 4A, 4B, 4C, and 5 such that there is an equal distribution among the categories. Patients will continue to be enrolled across all BI-RADS categories until the necessary number of cases with cancer has been acquired.

Study plan: Each enrolled participant will receive both a CESM and MRI exam ***prior*** to the breast biopsy. If the CESM has already been done as part of standard of care within 3 months ,

then only the MRI will be performed. If the MRI has already been done as part of the standard of care within 3 months, then only the CESM will be performed. If neither has been performed already, then both exams will be performed prior to the biopsy, to occur within 3 months of each other and the biopsy.

Given that CESM and MRI are FDA approved for diagnostic imaging, and are used in our clinical practice, all CESM and MRI studies performed will be interpreted by the clinical radiology staff and clinical reports will be generated in the online medical record. The participant will be contacted by her referring physician with imaging results, per clinical practice.

There should no delay of the subsequent breast biopsy. As of now, patients receive biopsies within one week of their diagnostic imaging. This should not change with the initiation of this study. We will be performing the breast MRI on the hospital's research scanner, so we will not be limited by the clinical MRI schedule, and should be able to schedule this fairly quickly. The CESM is similar to a diagnostic mammogram and is very easy to add into the routine clinical schedule.

Follow-up: No dedicated follow-up research visits are necessary. However, follow-up visits per clinical care may occur, although they are rare. Given that these patients are all diagnosed with breast cancer, there is a strong attempt to address all imaging findings before treatment. In addition, given that patients will have had received both MRI and CESM, it is even less likely that there will be a finding seen on CESM that it not seen on breast MRI and addressed before treatment. As a result, there is a very small chance for a CESM only finding. If this should occur, the finding will be addressed prior to treatment, if there is a high concern for malignancy. If the likelihood of cancer is felt to be low and tissue sampling can't be performed, then a follow-up CESM may be recommended.

1.1.3 Case Collection and Categorization:

Prospectively acquired imaging sets of CESM and MRI will be added to existing cases that were previously acquired through previous research, clinical cases, and external cases. All imaging sets will be categorized as negative, biopsy proven benign, or biopsy proven malignant.

1.1.4 Reader Study:

Imaging sets of CESM and MRI will be randomly selected from the three groups of cases (negative, biopsy proven benign, and biopsy proven malignant) to create an enriched reader set for retrospective review with a proportion of cases as outlined in Figure 1 of the schema, reproduced below. 88 negative/benign cases and 44 cancer cases will be randomly selected.

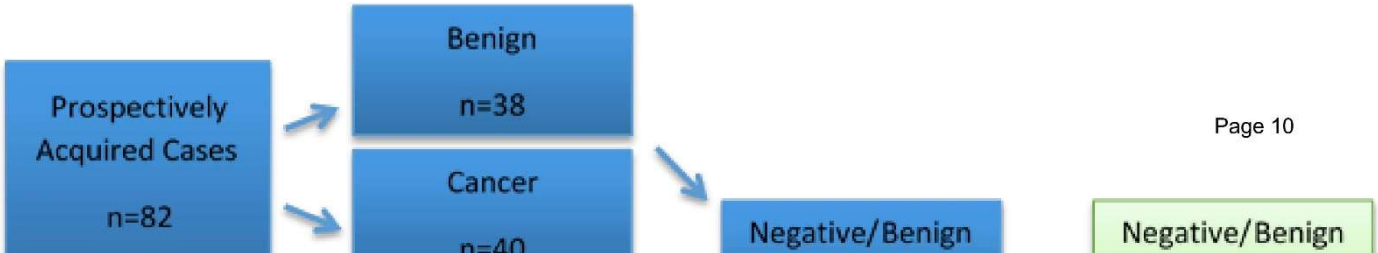

Figure 1. Reader Study. Prospectively acquired imaging sets will be added to existing cases for the case collection. Types of cases and the number of cases to be recruited are presented. Cases to be used for the reader study are shaded green.

Radiologist Readers: 13 radiologists will participate in this study. Radiologists who are in fellowship training for breast imaging or those who are MQSA certified to interpret mammography exams are eligible as long as they can commit to interpret all imaging within the study case set.

Readers that are also co-investigators will not be paid, as this will present a conflict of interest. Only readers who are not co-investigators will be paid. It is appropriate to pay them as the reader study will take a significant amount of their time and we will not be able to recruit readers without compensating them appropriately.

Recruitment: We intend to recruit internal DF/HCC radiologist readers. We will only recruit non-DF/HCC readers if the number of internal readers identified does not suffice. In the event that external readers are needed, we will execute a Data Usage Agreement prior to their participation on the study . To identify radiologist readers, an email will be sent out to Breast Imaging radiologists at academic centers in Boston. This email will describe the study and commitment required of the readers. Readers will be provided an honorarium for participation or will be authors on papers generated. Verbal or email affirmation of an interest in participation to the research coordinator will serve as informed consent. No documentation of informed consent will be provided for this study as this study presents no more than minimal risk and the performance of imaging interpretation is within their scope of clinical practice for which informed consent would not routinely be necessary. The study coordinator will schedule time for the radiologist readers to complete the required case reads for the reader study. Their name, experience reading breast MRI, and experience reading CESM will be collected at the time of enrollment at which time they will be given a reader ID number. The readers' interpretations of the imaging sets will be performed anonymously using their reader ID numbers.

Training Cases: All readers who have interpreted less than 30 CESM cases, either as part of prior research or clinical practice, will receive a background presentation on CESM and will complete a training set of 30 CESM cases prior to beginning the reader study. These cases will include cancer and non-cancer cases. Answers will be provided for these cases prior to the start of the formal reader study. In addition, all readers will be trained on the conduct of the study to include 5 cases of how to interpret and record their interpretations.

Image Interpretation: Each of the 132 cases comprising the study set will have both a CESM and MRI. Half of the readers will read the 132 CESM cases first (called the CESM study session) and then will read the 132 breast MRI cases (the MRI study session). The other half will do the reverse, and will interpret the MRI cases first followed by the CESM cases. There will be a month wash-out period between the two sessions. Each reader will independently review and score each of the images.

A. CESM session: - Review and score the low energy images (these images are equal to conventional 2D mammographic images); this will be the MG score

- Then review and score the low energy images combined with the subtraction images (this is the CESM exam); this will be the CESM score.

B. MRI session: - Review and score the abbreviated MRI sequences (these are a subset of the full protocol); this will be the abMRI score. - Then review and score the complete MRI exam; this will be the MRI score.

The order of image presentation per reader is randomized. Half will complete the CESM session first and the other half will complete the MRI session first. Cases will be randomized and counterbalanced to account for learning, experience, and fatigue that occur during reader studies. Readers and study assistants will be blinded to the details of the investigational site, subject history, previous mammography images, and previous clinical results. The radiologist reader will provide a forced BIRADS score of 1,2,3,4a, 4b, 4c, or 5 defined, respectively, as negative, benign findings, probably benign findings, low suspicion for malignancy, moderate suspicion for malignancy, high suspicion for malignancy, and highly suggestive of malignancy associated with probability of malignancy of (0%), (0%), (::=::2%), (>2% to ::=;10%), (>10% to ::=;50%), (>50% to <95%), and (95%), respectively. Each case will also be scored for confidence in diagnosis on a 5-point Likert scale using strongly confident, confident, neutral, not confident, and strongly not confident. This will be the confidence score. Readers will report their interpretations into RedCap database using reader ID numbers and the results will be analyzed anonymously.

The reader study will take place after all the imaging studies have been acquired and reported. Consensus will not be necessary for the reader study. We will be evaluating individual and group ROC curves.

1.2 Primary Objectives

To determine whether CESM is non-inferior to breast MRI for breast cancer screening

1.3 Secondary Objectives

To determine whether CESM is non-inferior to abbreviated breast MRI for breast cancer screenmg

1.4 Third Objectives

To determine whether CESM is superior to mammography for breast cancer screening

1.5 Fourth objective

To determine patient preference for breast MRI versus CESM for breast cancer screening

2. BACKGROUND

2.1 Study Disease(s)

The limitations of conventional mammography, with its inability to detect breast cancers in dense breast tissue and subsequent reduced sensitivity, are now well-established and have resulted in new legislation in nearly 50% of US states requiring reporting breast tissue density to patients and recommending supplemental imaging screening with ultrasound and MRI. The decreased sensitivity is especially concerning in the intermediate and high-risk groups (6-11). MRI has become the prime alternative in these groups but has its own limitations including increased false positives associated with unnecessary biopsies and anxiety, increased cost, increased time, and decreased availability at many centers (12). Ultrasound is another, less commonly used alternative as it is associated with even more false positives than MRI, is time intensive, and operator dependent.

CESM is a new imaging tool using a dual-energy technique that has been shown in the diagnostic setting to have increased sensitivity for breast cancer detection relative to conventional 2D imaging and equal sensitivity with improved specificity relative to breast MRI. It was FDA approved for diagnostic imaging in 2011. It requires no additional time relative to conventional 2D imaging other than IV line placement and contrast administration and is overall faster than breast MRI. It is less expensive than breast MRI as it is currently being billed as a diagnostic mammogram and is easier to implement into practice than MRI given that it is simply a software upgrade to commonly used mammography equipment and the staff training is minimal.

Given these benefits, CESM may prove to be useful in the screening setting, where traditional imaging tools including 2D imaging, MRI, and ultrasound have shortcomings. This is especially important for those patients who cannot get the more traditional imaging. However, CESM's value in screening has not yet been established. This will be the first reader study that evaluates CESM's role for screening relative to 2D mammography and MRI.

Abbreviated MRI is a new method of perfonning MRI in which only the critical sequences of the complete MRI exam are acquired and used for interpretation, shortening the overall time of the exam. The images that are acquired are those that are considered vital for MRI interpretation and preliminary studies have shown that abbreviated MRI has similar performance to routine MRI (13-16). As a result, programs are considering using abbreviated MRI protocols for

screening to decrease the time and potentially the cost of the MR exam. Given that the abbreviated protocol may replace MRJ in the future, it is important to determine how CESM compares with it as well when considering whether CESM can replace MRJ.

2.2 Correlative Studies Background

NIA

3. PARTICIPANT SELECTION

Given that this study involves an FDA approved imaging test that is used in clinical care with a well established risk profile, and does not involve a therapeutic agent or investigational device, informed consent will be performed by any member of the study team, including the study coordinator.

3.1 Prospective Patient Recruitment

3.1.1 Inclusion Criteria:

- Women
- Age > or equal to 30 years
- Recommendation for breast biopsy has been made
- Recommendation for biopsy will result from an imaging work-up originating with a screening exam (mammogram, tomosynthesis, ultrasound, or MRJ) that was within 3 months of biopsy.

3.1.2 Exclusion Criteria:

- Men
- Women with implants

- Participants who have a known allergy to contrast media.
- Participants who have a known severe allergic response to one or more allergens, defined as anaphylaxis
- Participants with poor asthma control using the National Heart, Lung, and Blood Institute guidelines as defined by:
- Symptoms > 2 days per week
- Short-term beta agonist use > 2 days per week
- Nighttime awakenings > 2 times per month
- Participants with Renal insufficiency or failure, as determined by GFR calculation. Given that GFR is reported as a range, the majority of the reported range must be 60 mL/min/1.73m^2. GFR must be measured for all patients within 24 hours of the 1magmg exams.

- Participants who are pregnant. Pregnant women are excluded from this study due to the radiation dose from the CT scan and its potential teratogenic effects on the fetus.
- Participants who are breastfeeding are excluded because there is an unknown but potential risk for adverse events in nursing infants secondary to contrast administration in the mother.
- Participants with the following underlying medical conditions: multiple myeloma, myasthenia gravis, dysproteinemias, severe cardiac disease, aortic stenosis, primary pulmonary hypertension, cardiac arrythmia, or severe cardiomyopathy . These underlying medical conditions may make the participant more likely to develop a contrast reaction.

This is based on the ACR contrast manual version 10.3 and hospital policy.

- Participants with a concurrent active illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, thyroid storm.
- Participants with thyroid carcinoma or thyroid disease for whom systemic radioactive iodine therapy is part of planned diagnostic work-up or treatment within 2 months following the contrast mammogram study.
- Participants with non-MR compatible objects or implants that would make MRI a contraindication.
- Participants who have a pacemaker, pacer wires, implantable defibrillator, or implanted monitoring device.
- Participants with intracranial clips, metal implants or external clips within 10 mm of the head.
- Participants who have had a metal injury to the eye.

3.2 Reader Study

3.2.1 Inclusion Criteria:

- CESM and MRI exam performed within 3 months of one another.
- CESM and breast MRI exams must be performed as part of imaging work-up based on a screening exam of any type (mammography, tomosynthesis, ultrasound, and MRI)
- CESM studies will include at least four low energy and four recombined images

(LCC, LMLO, RCC, RMLO).

- MRI exams will include at least fluid sensitive sequence, multi-phase Tl-weighted images

3.2.2 Exclusion Criteria:

- Imaging sets with implants.
- Imaging sets in which a biopsy or surgical intervention was performed since the most recent screening exam, prior to acquisition of the study MRI or CESM.
- Imaging sets in which a biopsy was recommended, but biopsy was not performed and 2 year imaging follow-up is not available.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION

4.1 Prospective Patient Recruitment

4.1.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of study imaging. Any participant not registered to the protocol before study imaging begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol imaging following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.1.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP#: REGIST-101) must be followed.

4.2 Reader Study

Radiologist readers will be recruited from the local community to participate in the retrospective reader study. Verbal or email affirmation of an interest in participation to the research

coordinator will serve as informed consent. Radiologist readers will then be enrolled in the study by a member of the study team. Information on radiologist readers will be kept in RedCap.

5. TREATMENT AND/OR IMAGING PLAN

5.1 Prospective Patient Recruitment

Patients will be recruited after a biopsy has been recommended. Each enrolled participant will receive both a CESM and MRI exam ***prior*** to the breast biopsy. If the CESM has already been done as part of standard of care within 3 months, then only the MRI will be performed. If the MRI has already been done as part of the standard of care within 3 months, then only the CESM will be performed. If neither has been performed already, then both exams will be performed prior to the biopsy, to occur within 3 months of each other. All CESM and MRI studies performed will be interpreted by the clinical radiology staff. The participant will be contacted by her referring physician with imaging results, per clinical practice.

5.1.1 Pre-Treatment Criteria

5.1.1.1 GFR 2:60 per the clinical protocol. If a GFR is not available, then a point of care renal function test will be performed and reviewed on the day of the exam before the patient receives the CESM and/or MRI.

5.1.1.2 Negative urine pregnancy test. If the patient is of child-bearing potential, then this will be performed and reviewed on the day of the CESM and/or MRI before the patient receives the exam.

5.1.2 Duration of Follow Up

No additional dedicated research visits are necessary. Participants will be followed for 2 years through review of their chart to determine whether they developed breast cancer. Participants without follow-up or death will be considered lost to follow-up.

The deidentified imaging data may be used for future undefined research. This has been included in the informed consent document.

5.1.3 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore

6. DOSING DELAYS/DOSE MODIFICATIONS

NIA

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Patient Prospective Recruitment

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Given that the contrast mammogram and breast MRI will be acquired according to standard of care techniques without alterations in duration, contrast agent, or contrast type and given that the AE profile for these imaging exams are well established, we will not be capturing AEs for the purposes of analysis. We intend to only capture AEs for those patients who initiate phone calls to our department. Should a patient contact the research team, the Pl or co-investigator will evaluate and decide the best management, to include referring patient to the primary care physician for further management or sending patient to the emergency department.

The following list of reported and/or potential AEs (Section 7**.1)** and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Expected Toxicities for CESM

Risk of toxicity is related to the contrast agent that is administered during the imaging exam. Risks include allergic, allergic-like, or physiologic type of reaction to the contrast agent. There is also the risk for contrast induced nephropathy.

There is also a risk for contrast extravasation at the time of contrast administration. Per the ACR Contrast manual v l0 .3 "the reported incidence of intravenous (IV) contrast media extravasation related to power injection for CT has ranged from 0.1% to 1.2%. Extravasated iodinated contrast media can result in injury to surrounding tissues, particularly to the skin, producing an acute local inflammatory response may not peak for 24 to 48 hours. The vast majority of patients in whom extravasations occur recover without significant sequelae. Only rarely will a lowosmolality contrast media (LOCM) extravasation injury proceed to a severe adverse event."

Common reactions to extravasation include initial swelling or tightness at the injection site, and/or stinging or burning pain. On physical examination, the extravasation site may be edematous, erythematous , and tender. More severe injuries include compartment syndrome, tissue ulceration, and tissue necrosis.

Risk of toxicity is also related to the risk of biologic harm from radiation administered during the exam. However, this risk is non-measurable during the course of this study.

7.1.2 Expected Toxicities for MRI

Risk of toxicity is related to the contrast agent that is administered during the imaging exam. Risks include allergic, allergic-like, or physiologic type ofreaction to the contrast agent. There is also the risk for contrast-induced nephropathy and nephrogenic systemic fibrosis.

There is also a risk for contrast extravasation at the time of MRI contrast administration. The ACR contrast manual states that " gadolinium-basedMRI contrast media have similar to lower toxicity in comparison to iodinated contrast agents; however, extravasations of these agents usually do not cause severe injury, likely due to the smaller total volumes of contrast material that are injected at MRI."

During the MRI, the subject will receive an injection of a contrast made up of an element called gadolinium. A possible side effect is that some people experience nausea, diarrhea and headache. Contrast agents with gadolinium have been known to cause a severe skin disease in people who already have some degree of kidney failure. This is known as Nephrogenic Systemic Fibrosis (NSF). It can cause a widespread stiffening of the tissues in the body. While the precise cause of this disorder remains a mystery, it generally occurs in patients whose kidney function is so limited that they require dialysis. A blood test will be taken prior to the MRI in order to determine the subject's kidney function. Known renal problems are reasons to exclude subjects from thisstudy.

The United States Food and Drug Administration (FDA) issued a warning about the risk of brain deposits following repeated intravenous use of gadolinium-

based contrast agents (GBCAs) for MRI. After being administered intravenously, GBCAs are mostly eliminated from the body by the kidneys. Trace amounts of gadolinium, however, may stay in the body long-term and are known to be deposited in the skin, bone, and brain. Recent studies conducted in people and animals have confirmed that gadolinium can remain in the brain after intravenous administration, even in individuals with normal kidney function. Available information at this time does not show any adverse health effects related to the deposits in the brain.

The risk of serious adverse reactions to intravenous MRI contrast agents is very small (~7 / 5,000,000). In the unlikely event of an adverse reaction, physician and nursing staff are available to evaluate and if necessary, treat patients. One of the more severe, but extremely rare, risks is that of anaphylaxis (a severe allergic reaction that can cause breathing difficulties and/or low blood pressure). A resuscitation cart is on site with all materials essential for urgent treatment in the unlikely event of an anaphylactic reaction. Finally, the institution has a standard procedure to alert a special team designated to respond to patients with life-threatening emergencies should further assistance be needed.

7.1.3 Other Risks for MRI

All MRI studies performed under this protocol will not exceed the FDA guidelines for magnetic resonance in any way. As in the circumstances of all MRI scanning, the single greatest risk of MRI for subjects is the possibility of a ferromagnetic object flying towards the magnet and hitting the subject while the subject is in the scan room. Depending on the object size and shape, the potential for harm could be great. In order to assure against such an event, all persons present at the study (subject, investigators, technicians, etc.) are screened for metal objects which are removed and placed in a safe location away from the magnet room. In the event an accident or incident of any kind should occur while the subject is in the MRI Center or the magnet, all investigators and associated staff are trained in calling codes and performing CPR. Emergency procedures have been established and a manual containing these procedures is kept in the console room.

MRI machines are long narrow, cylindrical tubes which can cause a feeling of claustrophobia or panic in some patients. If patients suffer from claustrophobia, they will be excluded from the study. The technologist performing the scan will have voice contact with the subject while they are in the MRI scanner. If the subject feels the need to be removed from the MRI scanner at any time, then the scan will be stopped immediately.

7.1.4 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found

in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment /electronic applications/etc.htm.

- **For expedited reporting purposes only:**
  AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  Definite - The AE *is clearly related* to the study treatment.
  Probable - The AE *is likely related* to the study treatment.
  Possible - The AE *may be related* to the study treatment.
  Unlikely - The AE *is doubifully related* to the study treatment.
  Unrelated - The AE *is clearly NOT related* to the study treatment.

7.1.5 Expedited Adverse Event Reporting

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.1.6 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

	OF/HCC Reportable AEs				
Attribution	Gr. 2 & 3 **AE Expected**	**Gr. 2 &3AE Unexpected**	**Gr. 4AE Expected**	**Gr.4AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					

* For participants enrolled and actively participating in the study ***or*** for AEs occurring within

30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.

7.1.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.1.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.2 Reader Study

There are no expected AE related to the reader study.

8. IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

9. STUDY CALENDAR

9.1 Prospective Patient Recruitment, Year 1

	Visit [1a,b]
	Screening &exam
Informed Consent	X
Medical History	X
Urine pregnancy Test	Xe
Blood Test	Xct
Contrast Mammogram	Xe
Breast MRI	Xe

Patient Experience Survey	Xr
!Breast Biopsy	X

a If abnormal findings are detected on the contrast mammogram or breast MRI, there is the potential that additional standard of care tests and procedures will need to be performed. These may occur on the same day or at a later date.

b The contrast mammogram and the breast MRI may be performed on the same day or on different days. They may also be performed on the same day or a separate day from the breast biopsy.c For patients who are of child-bearing potential, and having both MRI and CESM performed on the same day, they will receive a single pregnancy test immediately before the imaging tests are performed. If the studies are not performed on the same day, then they will have a pregnancy test before each of the imaging tests on the day of the imaging exams. ct For patients having both MRI and CESM performed on the same day, they may need to get blood work testing how their kidneys work. This will happen once immediately before the imaging tests, on the day of the imaging exams. If the MRI and CESM are performed on different days, they may need blood work before each imaging test.e If either the contrast mammogram or the breast MRI are performed as part of standard of care, then they will be billed to insurance. If they are performed for research purposes only, then they will be billed to the grant. fThe patient experience survey will only be given once after the second of the two imaging tests has been performed.

9.2 Reader Study, Year 2

	Months 0-12	Month 13-15	Month 16	Months 17-19	Months 20-22	Months 23-24
Prospective Image acquisition	Xxx					
Image Categorization		Xxx				
Training Session			xxx			
Reader Study - session I				xxx		
Reader Study - session 2					xxx	
Data analysis						xxx
Report						xxx

10. MEASUREMENT OF EFFECT

10.1 Reader Study

Each reader will interpret 150 CESM and 150 MRI cases in two sessions, separated by a one month washout period. Each reader will independently review and score each of the image sets of the Reader Study Case Set. The method for interpretation is below:

A. CESM session:

--+ Review and score the low energy images (these images are equal to conventional 2D mammographic images); this will be the MG score

--+ Then review and score the low energy images combined with the subtraction images (this is the CESM exam); this will be the CESM score.

B. MRI session:

--+ Review and score the abbreviated MRI sequences (these are a subset of the full protocol); this will be the abMRI score. --+ Then review and score the complete MRI exam; this will be the MRI score.

The order of image presentation per reader is randomized. Half will complete the CESM session first and the other half will complete the MRI session first. Cases will be randomized and counterbalanced to account for learning, experience, and fatigue that occur during reader studies. Readers and study assistants will be blinded to the details of the investigational site, subject history, previous mammography images, and previous clinical results. The radiologists will score each case with a BIRADS (Breast Imaging Reporting and Data System) score of l,2,3,4a, 4b, 4c, or 5 defined, respectively, as negative, benign findings, probably benign findings, low suspicion for malignancy, moderate suspicion for malignancy, high suspicion for malignancy, and highly suggestive of malignancy associated with probability of malignancy of (0%), (0%), (:S2%), (>2% to :Sl0%), (>10% to :S50%), (>50% to <95%), and (2:95%), respectively. Each case will also be scored for confidence in diagnosis on a 5-point Likert scale using strongly confident, confident, neutral, not confident, and strongly not confident. This will be the *confidence score.* Readers will report their interpretations into RedCap database using reader ID numbers and the results will be analyzed anonymously.

10.2 Other Response Parameters

Information on patient preferences of CESM versus MRI will be recorded using a survey in RedCap

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Prospective Patient Recruitment

11.1.1 Data Reporting

Patients will be registered in the Oncore system. Study patient data will be captured in an institutional RedCap system designed and maintained by the study team.

11.1.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.2 Reader Study

Data reporting will be entered into an institutional RedCap system designed and maintained by the study team

11.3 Multicenter Guidelines

NIA

11.4 Collaborative Agreements Language

NIA

12. STATISTICAL CONSIDERATIONS

This is a retrospective reader study to compare screening MRI and contrast enhanced spectral mammography for breast cancer screening, for which some cases will be prospectively collected.

12.1 Study Design/Endpoints

Exams will be interpreted by 13 radiologist readers. Each reader will score each CESM and MRI exam according to the Breast Imaging-Reporting and Data System (BI-RADS), ranging from 1-5. The score used will correspond to the most suspicious finding in the study. The primary outcome will be whether the exam is benign or malignant. BI-RADS scores 1, 2, and 3 associated with the corresponding categories of negative, benign findings, and probably benign findings will be negative (benign). BI-RADS scores 4 and 5 associated with the corresponding categories of suspicious and highly suspicious for malignancy will be positive (malignant).

Positive truth will be determined by histopathology confirming malignant pathology. If a woman has had both a percutaneous breast biopsy and surgical excision, the worst pathology will be considered for analysis.

Negative truth will be considered for all cases categorized as negative or biopsy proven benign. All cases will require two-year follow-up to confirm the absence of malignancy. The follow-up will take the form of any documentation of the woman's health to include the online medical record (OMR) or imaging archival system, or direct communication with her.

At the time of the reader study, there may be cases classified as negative that have not had complete follow-up since their initial CESM and MRI exams. These cases will be reevaluated after the reader study has been completed to confirm whether the cases represent false negatives. This will be accounted for in the subsequent analysis. Given that the false negative rate of MRI is low and approximates 3%, it is unlikely that this will impact the analysis significantly (17).

We will compare the BI-RADS score of CESM and MRI with the final outcome of negative or positive truth to determine the area under the curve for each technology for ROC analysis.

12.2 Sample Size, Accrual Rate and Study Duration

Objective 1: To compare the diagnostic accuracy of CESM with breast MRI for detection of breast cancer.
Area under the ROC curve (AUC) of CESM and MRI will be calculated for each of the 13 readers and compared with Delong & Delong (1988)'s method within each reader. The reader average AUC will be calculated for each modality and the difference between the modalities and its associated 95% confidence interval will be calculated using Obuchowski's method.

Objective 2/3: To compare the diagnostic accuracy of CESM with abbreviated MRI for detection of breast cancer.
Area under the ROC curve (AUC) of CESM and abbreviated MRI will be calculated for each of the 10 readers and compared with Delong & Delong (1988)'s method within each reader. The reader average AUC will be calculated for each modality and the difference between the modalities and its associated 95% confidence interval will be calculated using Obuchowski's method.

Objective 4: Descriptive statistics will be used to evaluate patient responses to the survey

Sample Size Justification: The analysis aims to test the non-inferiority of CESM when compared to MRI by establishing no loss of value in the ROC AUC. The null hypothesis is HO: (Reader average AUCCESM- reader average AUCMRI) :S -0.05 versus the alternative HA: (reader average AUCCESM-reader average AUCMRI) > -0.05. The test is based on a 2-sided 95% confidence interval on the difference between the reader average AUCs.
The ROC power and the sample size calculations are based on the methods of Zhou, Obuchowski and McClish.

Assuming the average AUC of the two modalities is 0.83, the correlation for same reader, different modalities is 0.47, correlation for different reader, same modality is 0.44, correlation for different reader, different modalities is 0.4 and correlation for group of readers, different modalities is 0.8. The interobserver variability is 0.002 and the intraobserver variability is 0.0004. The pooled readings from 13 readers on 44 cancer cases and 88 non-cancer cases will have at least 80% power to reject the null hypothesis that (AUCCESM - AUCMRI) S -0.05 with a 95% 2 sided confidence interval on the difference. The lower end of the confidence interval for the difference (AUCCESM - AUCMRI) must be greater than -0.05 to accept the alternative hypothesis of non-inferiority.

Accrual Targets for Prospective Recruitment			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	5		
Not Hispanic or Latino	77		
Ethnic Category: Total of all subjects	82 (A1)	(B1)	(C1)
Racial Category			
American Indian or Alaskan Native	0		
Asian	8		
Black or African American	8		
Native Hawaiian or other Pacific Islander	0		
White	66	11	
Racial Category: Total of all subjects	82 (A2)	(B2)	(C2)
	(A1= A2)	(B1= B2)	(C1 = C2)

12.3 Stratification Factors

NIA

12.4 Interim Monitoring Plan

There are no plans to conduct interim monitoring unless requested by the DSMC (see section 11.2).

12.5 Analysis of Primary Endpoints

See sections 12.1 and 12.2

12.6 Analysis of Secondary Endpoints

See sections 12.1 and 12.2

12.7 Reporting and Exclusions

NIA

13. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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