Comparing restriction spectrum imaging (RSI) to conventional and abbreviated breast MRI for breast cancer screening

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BACKGROUND/RATIONALE

Breast cancer is one of the most common cancers affecting women in the United States, where it accounts for 29% of newly diagnosed cancers and where one in eight women will be diagnosed with breast cancer in her lifetime.[1] Breast cancer remains a leading cause of cancer death in American women despite the proven mortality benefits of screening mammography (MG).[2-5] However, the sensitivity of cancer detection through MG in younger, premenopausal women, women with dense breasts, and women with genetic risk factors for breast cancer is significantly lower.[6-14] DCE-MRI, with sensitivities ranging from 75-100%[10,13,15-19] and a supplemental yield of 14.7 cancers per 1000 women screened,[20] is currently recommended by the American Cancer Society as a supplemental screening test for women with a high (>20%) lifetime risk of breast cancer. However, adding MRI also decreases specificity and increases the number of false positives and biopsies performed.[10,20-21] While DCE-MRI does not require radiation, it suffers from intravenous (IV) contrast-related safety concerns and also takes longer to perform, important considerations for screening.

(i) DWI improves screening breast DCE-MRI but is still limited: DWI requires no IV contrast and improves tumor conspicuity and the positive predictive value when added to screening DCE-MRI[22]. DWI also improves differentiation between benign and malignant breast tumors, probably because diffusion generally decreases in highly cellular malignant breast tumors.[23-28] A retrospective study involving 93 patients showed that adding DWI to DCE-MRI also decreased the false positive rate from 36% to 25%.[24] Recently, in women with dense breasts with occult cancers, DWI with *unenhanced* rapid MRI (FSE T2 and T1 sequences only) was shown to decrease the number of false positives when added to screening MG with a specificity of 91% but a sensitivity of only 45%, which is thought to be related to smaller tumor size since the average median tumor size was 14 mm compared to 20 mm in other studies.[29] Therefore, while adding DWI improves DCE-MRI cancer detection, smaller lesions may still be missed, probably secondary to distortion from b0 inhomogeneity and variable background breast parenchymal enhancement.[25]

(ii) RSI improves tumor conspicuity in prostate and brain: RSI is a type of advanced diffusion technique developed at UCSD that has been shown to address limitations of conventional DWI in prostate and brain by using a broad spectrum of diffusion sampling, novel mathematical modeling to separate the two main types of diffusion signal ("hindered diffusion" in extracellular space and "restricted diffusion" in tumor), and spatial distortion correction.[30-31] Retrospective studies at UCSD have now shown that RSI improves tumor conspicuity relative to ADC, can correct for b0 inhomogeneity, and can provide an *in vivo* cellularity map in prostate[32-36] and brain.[37-38] A recent pilot *prospective* study in prostate showed that adding RSI markedly improved detection of pT3 prostate cancer, detecting 8 of 9 cancers compared to 2 of 9 cancers with MRI alone.[34]

(iii) RSI in breast MRI: RSI may be beneficial in the breast, similar to conventional DWI, to

help distinguish benign and malignant solid tumors. RSI may also help better localize cancers specifically in the breast where images are more susceptible to distortion from b0 inhomogeneity secondary to larger air-tissue surface area, non-spherical breast shape, and breast offset from the center of the field, and where background parenchymal enhancement is known to be influenced by edema/hemorrhage, lactation, and hormones. Recent work at UCSD demonstrates that RSI b0 inhomogeneity correction can also be applied to standard breast imaging DWI, and work is currently being conducted to compare the effect of RSI to ADC in evaluating tumor response to chemotherapy in a sub-cohort of patients from the I-SPY2 trial.

RSI does not use IV contrast, thereby potentially providing a safer option for patients given the risk of nephrogenic systemic fibrosis and the uncertain effects of gadolinium on the brain.[39-43] Women who undergo annual MRI for breast cancer screening start younger than lower risk women, and recent breast density notification laws in some states may eventually lead to increased use of breast MRI for supplemental screening in patients with dense breasts by MG.

Given that RSI has a fast acquisition time (less than 5 minutes), can be easily standardized and normalized, does not use IV contrast, and can substantially improve conspicuity of even small tumors, RSI is a suitable candidate for breast cancer screening MRI. The applicability and diagnostic accuracy of RSI either alone, with abbreviated unenhanced MRI, or as a supplement to conventional DCE-MRI has not yet been evaluated. Few studies have examined the possibility of performing DWI without DCE-MRI. A retrospective study found that DWI with an abbreviated non-contrast MRI (DWI+T2-weighted images only) improved cancer detection in asymptomatic women with non-palpable breast cancer compared to MG alone, although improved detection was still lower than that of DCE-MRI.[44] More recently, DWI with an abbreviated non-contrast MRI (DWI+FSE T2+T1-weighted images only) was shown to significantly improve cancer detection in women with dense breasts (high-risk) who had a negative screening MG and clinical exam compared to DCE-MRI.[29] RSI, too, was recently shown to improve cancer detection, at least in prostate, when added to T2-weighted images only [36].

We propose an imaging reader study to evaluate the diagnostic accuracy of RSI compared to conventional contrast-enhanced MRI for breast cancer screening. We will specifically test the hypothesis that RSI is non-inferior to DCE-MRI+DWI for breast cancer screening by collecting cases from an enriched screening population. As a secondary aim, we will also evaluate the diagnostic accuracy of RSI compared to Ab-MRI for breast cancer screening since Ab-MRI has promise to eventually replace conventional breast MRI and is faster to perform.[45-49]

The funding provided by the Radiological Society of North America (RSNA) grant will allow us to collect the additional cases needed for a multisite reader study that will be funded through additional resources provided by the Department of Radiology at BIDMC. The goal of the reader study is to compare the diagnostic value of RSI with that of DCE-MRI+DWI and of Ab-MRI. If we are successful, future clinical testing could be done to determine whether RSI could replace DCE-MRI+DWI as an effective and fast method of breast cancer screening that does not use IV contrast.

PRELIMINARY STUDIES

Dr. Rakow-Penner and her colleagues at UCSD, who will be collaborators on this proposed study, have recently applied RSI to the breast under her RSNA resident grant with promising results. They retrospectively evaluated 11 patients from the UCSD cohort of the ISPY-2 clinical trial with a new diagnosis of breast cancer (biopsy-proven, high and low grade). They used DCE-MRI, standard DWI (b=0, 800 s/mm^2) and RSI-MRI (b=0, 500, 1500, 4000 s/mm^2 in 6, 6, and 15 directions to generate RSI cellularity index (RSI-CI) maps that are then distortion corrected) and compared the ability of these three imaging protocols to evaluate the biopsy-proven cancers. Examples are demonstrated in four patients in **Fig 1**.

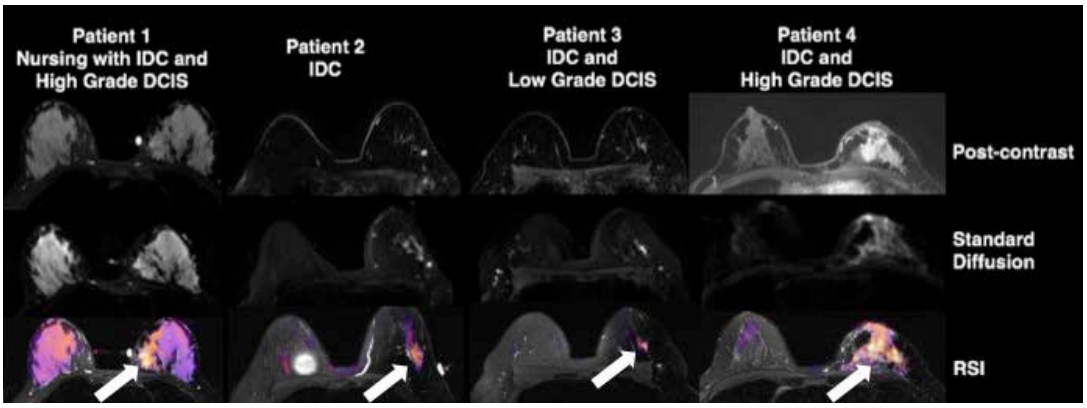

Figure 1. RSI detection of breast cancer. Images from post-contrast MRI, standard DWI, and RSI from 4 of 11 patients are shown. RSI-CI maps show increased tumor conspicuity in all patients in the region corresponding to the biopsy-proven cancer (arrows). Standard DWI identifies the cancer in Patient 2 but not in Patients 1, 3, or 4 (Row 2). Post-contrast MRI detects an 1 x 0.8 x 1.1-cm heterogeneous left breast mass with internal enhancement that correlates with the biopsy-proven cancer in Patient 2 and a 4.6-cm heterogeneously enhancing, spiculated left outer breast mass that correlates with the biopsy-proven cancer in Patient 4 (Row 1). However, post-contrast MRI only shows a minimally enhancing 8.3-cm non-mass enhancement above background in the left breast that corresponds to the area of biopsy-proven cancer in Patient 1 (Row 1; note that this same region in RSI is more conspicuous in Row 3) and fails to detect the cancer in Patient 3. The round white region in the right posterior inner breast on the RSI image in Patient 2 is artifact from the underlying T2-weighted image (Row 3). Data and figure are courtesy of Dr. Rakow-Penner.

The breast RSI-MRI protocol readily detected the breast cancer in all 11 patients. Standard DWI failed to definitively show the cancer in multiple patients (*e.g.*, patients 1, 3, 4, **Fig 1**). Contrast-enhanced MRI also did not detect all of the cancers (*e.g.*, patient 3), and cancer detection was less conspicuous, for example, in Patient 1 who was lactating and had higher background breast tissue enhancement and tumor enhancement that was only minimally above background (**Fig 1**). Results from these 11 patients also show that while mean ADC values from standard DWI did not statistically differ between cancer and normal tissue, the mean RSI-MRI Z-score values were statistically higher in the cancer tissue compared to the normal tissue, supporting that RSI-MRI improves tumor conspicuity as it does in prostate (**Table 1**).

Table 1. RSI Z-score and ADC in breast cancer and normal tissue. Mean RSI Z-score, ADC, and standard deviations for cancer and normal tissue in 11 women with recently diagnosed biopsy-proven breast cancer. The mean RSI Z-score was statistically higher in cancer compared to normal tissue. No statistical difference in mean ADC was found between cancer and normal tissue. Data and table are courtesy of Dr. Rakow-Penner.

	RSI Z-score		ADC	
	Cancer mean(st. dev)	Normal mean(st. dev)	Cancer mean(st. dev)	Normal mean(st. dev)
AVERAGE	13.4 (6.5) *	0.19(0.29)	1.2(0.2)	1.12(0.63)

OBJECTIVES/STUDY AIMS:

Primary Aim: To measure the diagnostic accuracy of breast restriction spectrum imaging (RSI) in comparison to conventional breast MRI (dynamic contrast-enhanced MRI with diffusion-weighted imaging; DCE-MRI+DWI) for breast cancer screening.

Secondary Aim: To measure the diagnostic accuracy of RSI compared to that of abbreviated MRI (Ab-MRI) in breast cancer screening.

ELIGIBILITY

Patient Participants

Inclusion Criteria

Women presenting for breast cancer screening with either MRI or mammography:

- *Group 1* will consist of women who present for screening breast MRI:

    1. Age ≥ 18
    2. Female
    3. Asymptomatic for breast disease
    4. Presenting for routine breast cancer screening with MRI

- *Group 2* will consist of women who presented for a screening mammogram (2D or 3D tomosynthesis) AND who have had a biopsy recommended after diagnostic workup:

    1. Age ≥ 18
    2. Female
    3. Initial presentation for routine breast cancer screening with mammogram (2D or 3D tomosynthesis) and/or ultrasound *and* biopsy recommended after subsequent diagnostic workup (BI-RADS 4 or 5)

Exclusion Criteria

1. Known or suspected renal insufficiency, rendering the participant unable to safely receive intravenous contrast based on institutional clinical protocol. Renal insufficiency for the purposes of exclusion includes any of the following:
    - Known history of end stage renal disease with EGFR<30 mL/min/1.73m^2
    - Point of care (POC) measure of creatinine clearance (eGFR) prior to obtaining the MRI <35. *We will perform this POC test as needed per institutional policy for routine MRI if: (a) answered yes to any of the Choyke questions AND no creatinine result is available in the OMR within 30 days of the MRI exam, regardless of patient age, or (b) the patient is > 60 years old, or (c) the patient is on hydroxyurea.*

2. History of adverse or allergic-like reaction to gadolinium MRI intravenous contrast, rendering the participant unable to safely receive intravenous contrast based on institutional clinical protocol.

3. Presence of MRI unsafe devices or objects which would make having an MRI unsafe, as per institutional clinical protocol. MRI unsafe devices or objects for the purposes of exclusion include but are not limited to certain intracranial aneurysm clips, cardiac pacemaker, and implantable defibrillator devices, metallic heart valve, or coronary artery stents, breast tissue expanders, bio or neurostimulators, pellets and bullets, ocular implants and devices, otologic and cochlear implants. Other devices or metallic objects may be deemed unsafe for MRI at the radiologist's discretion.

4. Unable to tolerate exam (*i.e.,* secondary to untreatable claustrophobia, positioning constraints/unable to lie prone).

5. Body weight exceeds that allowable by the MRI table.

6. Breast biopsy or surgical intervention planned before the test RSI-MRI in this study.

7. Breast implants (silicone or saline).

8. Nursing or thinks she may be or is pregnant, as gadolinium contrast-enhanced MRI is unsafe. *We will perform a pregnancy test as needed per institutional policy for routine breast MRI*. Per institutional clinical protocol, all females of childbearing potential who are uncertain if they are pregnant or think they are pregnant must have a blood test or urine study within 2 weeks prior to the MRI exam to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or prior tubal ligation, who:
   - Has not had a hysterectomy or bilateral oophorectomy
     OR
   - Has not been naturally post-menopausal for at least 2 years (*i.e.,* has had menses at any time in the preceding 2 years).

Radiologist Reader Participant

Inclusion Criteria
1. Must have clinical experience in interpreting breast MRI.
2. Must have interpreted at least 10 breast MRI exams with RSI interpretation.

Exclusion Criteria
1. None.

SUBJECT ENROLLMENT

Patient Participants

All consecutive participants meeting the eligibility requirements will be enrolled in this study. We are requesting waiver of informed consent for women in Group 1 as we will only be collecting images and clinical report information acquired under standard of care imaging and procedures. Recruitment from Group 1 will continue through the end of the study until at least 40 total cancer cases from both groups have been acquired for the reader study. We will obtain a written, signed IRB-approved informed consent from women in Group 2 as the MRI to be performed would not ordinarily be a part of clinical care for women in Group 2.

Potential participants in Group 2 may be introduced to the study by either the breast imaging radiologist specialist seeing the patient for diagnostic workup and consultation, by the referring provider, or by independently looking at the study patient flier (Appendix) available in the consult room. An email and referring provider flier (Appendix) will be sent to referring providers to inform them of the study and eligibility criteria and to ask for their help to introduce the study to and recruit additional patients. The email to referring providers will also provide a means of continuity of care whereby the informed referring provider can further discuss the study with any patient who has already decided to enroll or who has questions about the study. The patient flier will also be provided to already consented participants. The study team will approach the patient regarding participation in the study upon approval from the breast imaging radiologist specialist seeing the patient or the referring provider, or if approached by the patient after independently seeing the patient flier available in the consult room for all patients.

STUDY DESIGN

We will conduct a reader study of RSI, DCE-MRI+DWI, and Ab-MRI imaging to test whether the diagnostic accuracy of RSI is non-inferior to that of DCE-MRI+DWI and Ab-MRI for breast cancer screening. The reader study is the mechanism that we will use to obtain statistically valid diagnostic accuracy results given the small number of cancers that we can access through our grant funding and through a screening population. Images for the reader study will be prospectively obtained from an enriched screening population. Funding from this grant will be used to recruit eligible women to undergo breast MRI, which includes RSI. These cases will supplement the cases obtained from women undergoing their high-risk clinical breast screening MRI exam (which also includes RSI) such that 40 cancer cases with MRI and RSI imaging sets are available for the reader study. The high-risk clinical MRI exams will be funded by clinical dollars (**Fig 2**).

Prospective case collection (Fig 2): Cases for the imaging reader study will be obtained from two screening groups to obtain 40 cancer cases for the reader study:

Group 1: **Screening MRI** (24-36 cancers expected).

Group 2: BI-RADS 4/5 findings after work-up originating from screening MG who will be recruited to undergo MRI as part of this study (Screening MG BI-RADS 4/5) (10 cancers expected of 30 imaged).

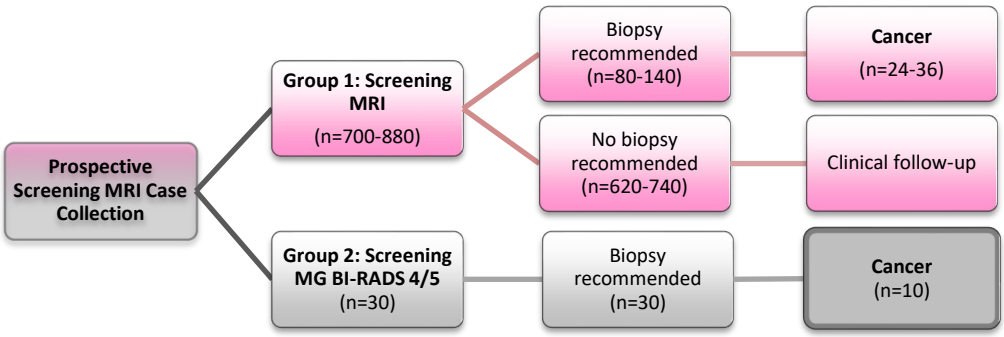

Figure 2. Prospective screening MRI case collection and funding. Conservative estimate of the number of cancers obtained from the prospective case collection of women undergoing breast MRI (all include RSI) derived from two breast cancer screening groups. **Group 1** (**pink boxes**): Clinical Cases. **Group 2** (**grey boxes):** Cases recruited for this proposal. Together, the cases from these two screening groups will form a reader study set of 40 biopsy-proven cancers (**solid pink boxes-Group 1 and solid grey boxes-Group 2**).

Women in Group 1 will be identified at the time of MRI screening, and consecutive cancer and non-cancer cases will be selected for the reader study. Since RSI is a type of diffusion imaging, the sequence can easily be incorporated into routine clinical screening MRI, thereby avoiding additional cost or time to women in Group 1. An additional group (Group 2) is included to *increase* the number of cancer cases available for our reader study so that we have 40 cancers altogether. These women will be identified at the time of completion of diagnostic imaging workup for a BIRADS 0 screening mammogram when a BIRADS 4 or 5 is assigned but *before* the patient undergoes biopsy. These women will be recruited into the study, and the RSNA grant will provide the funding to allow these women to obtain RSI and DCE-MRI+DWI prior to their scheduled biopsy at no additional cost to the patient. The estimated number of additional cancers detected by using this enrichment recruitment strategy is 10 cancers (based on an institutional cancer detection rate over the last 5 years of 4/1000, a positive biopsy rate of 30%, 10,000 yearly screening mammograms, and allocated budget). The estimated number of cancers obtained from Group 1 alone is 24-36 cancers.

The reference standard will be the most advanced pathology results for those participants who have received a biopsy and/or surgical excision and clinical follow-up for 1 year or more for those participants who have not received a biopsy before the end of this study. Follow-up to confirm the absence of malignancy in these patients will occur through review of the online medical record (OMR) and/or subsequent breast imaging.

Image acquisition: All enrolled participants will undergo imaging with: Standard-of-care DCE-MRI with Gadolinium including at least T2, pre-contrast fat- saturated T1, dynamic post-contrast fat-saturated T1, and kinetic angiomap analysis) with the patient in the prone position and using a dedicated multichannel breast coil on an 1.5T or a 3T magnet; (ii) standard DWI (at least b = 0, 800 s/mm^2); (iii) diffusion tensor imaging (multi-shell acquisition with range of b-values up to b = 4000 s/mm^2 in multidirections) to reconstruct RSI-CI z- score maps with a short sequence collecting data in the reverse phase encode direction at b = 0 s/mm^2 to permit distortion correction of standard diffusion and RSI-CI maps. From here on, since RSI is a DWI technique, adds no additional risk, and takes approximately 5 minutes (conventional breast MRI exam total time is currently approximately 30 minutes), the standard DCE-MRI with DWI and RSI will become a part of routine clinical breast MRI protocol and will be performed on all patients at BIDMC.

RSI technique and image post-processing: RSI is a novel, type of unenhanced advanced DWI sequence developed by our collaborators at UCSD with a built in distortion-correction technique that can be applied to any diffusion technique using echo planar imaging acquisition.[31,35] The breast RSI parameters will be added to the DCE-MRI+DWI exam, before the administration of IV contrast. RSI will be performed using pulsed-field gradient, spin-echo, echo planar imaging with "multi-shell" diffusion data (*i.e.,* multiple b-values up to b = 4000 s/mm^2 and multiple diffusion directions for all non-zero b-values). The b0 images will be collected in both the forward and reverse phase encoding directions to allow for post-processing correction of spatial distortion from magnetic field, b0 inhomogeneity, which is an inherent limitation of conventional DWI. Post-processing standardized RSI-CI maps can be derived from the RSI and axial T2-weighted images, as previously described.[32,35-36] Post-processing software will also correct for patient motion.

Our UCSD co-investigators have provided the necessary software, which has already been installed on our MRI scanner and reading workstations. They will work with the BIDMC team to set up RSI at BIDMC and will work to create RSI-CI images for the reader study. The generated post-processed images including RSI-CI maps will be sent to PACS/RIS via DICOM SCU/SCP for viewing. De-identified cases, along with the associated deidentified radiology report and final pathology will also be sent to UCSD via the BIDMC Secure File Transfer system (http://transfer2.bidmc.harvard.edu) or via mailed CDs for post-processing of images to create RSI-CI images for the reader study and to allow for continuous image processing quality assurance in this initial study; a Data Usage Agreement (DUA) will be executed for this purpose.

Patient Survey: There are two groups in this study. Group 1, are patients getting a routine screening MRI, and for whom a waiver of consent is requested. Group 2, are patients actively enrolled prior to their biopsy, and these patients are consented.

Patients who undergo a breast MRI for any reason (and may be/or may not be in Group 1 or Group 2) will be asked to take a brief survey once their MRI is complete, regarding their experience with the contrast injection and their view on breast cancer screening frequency. We request a waiver of informed consent for women who take this survey, as doing the survey is optional and if they agree to complete it, that is considered informed consent.

Image interpretation: Clinical breast imaging radiology staff will interpret and issue a clinical report for all DCE-MRI+DWI exams, shortly after the exam is performed, as per routine clinical practice guidelines for clinical breast MRI. RSI images will not be interpreted for clinical use and will not be in the standard issued clinical report. RSI images will also not be used to guide clinical management since the gold standard is currently DCE-MRI+DWI.

Additional information regarding study handling of unexpected findings and communication of findings is detailed under the "Regulatory" section of this protocol (page 12).

Reader study: The deidentified case sets will include negative, biopsy-proven benign, and biopsy-proven cancer cases drawn from both cohorts, as detailed in **Fig 2**. The reader study itself will be supported by departmental resources. The radiologist readers in the reader study are for the sole purpose of collecting reader interpretations for which to achieve our specific aims of evaluating the efficacy of RSI compared to contrast-enhanced breast MRI and

abbreviated breast MRI in breast cancer screening. We *will not* be studying how readers learn or what readers learn. The radiologist readers will be selected as consultants for their expertise in breast imaging based on American College of Radiology (ACR) training and accreditation guidelines for breast MRI interpretation.

(i) Case selection: 40 cancer and at least 70 non-cancer cases will be selected for use in the reader study. The non-cancer cases will be randomly selected from the available non-cancer case pool, stratified by important factors such as age, menopausal status, breast density, and background parenchymal enhancement to match the frequency of those factors in the cancer cases.

(ii) Reader training: All of the radiologist readers will be breast imagers *already trained and accredited* per the ACR guidelines in breast MRI interpretation, including diffusion weighted imaging (DWI). RSI is a *type* of DWI, but because the readers will not have had prior specific experience with RSI, we are going to *familiarize* them with interpreting this specific sequence. Dr. Rakow-Penner, our collaborator at UCSD who is experienced in the RSI technique, will familiarize the radiologist readers who will participate in the reader study with the RSI sequence. All potential readers will complete a training set of at least 10 benign and cancer RSI breast cases. Dr. Rakow-Penner will provide dedicated instruction and feedback via an online webinar. A set of test cases will be given only for the purposes of making sure all readers entering the reader study to have achieved a pre-set level of competence (set at 90% correct). Readers will be considered sufficiently trained once they successfully complete a test set of at least 10 cases (90% correct). Additional training and test cases will be provided as needed until enough readers have been sufficiently trained/achieved this level of competence. Once they have achieved this level of competence, the readers will be deemed qualified for participation in the reader study to evaluate RSI in breast cancer screening. Those who cannot fulfill the reader commitments will be unable to participate in the ready study.

(iii) Radiologist readers: Fifteen breast imaging radiologists from BIDMC and other Harvard and surrounding institutions' teaching facilities will be identified based on their possessing expertise in breast MRI interpretation based on the American College of Radiology (ACR) guidelines to participate in this study. An email will be sent out to breast imaging radiologists describing the study and determining their interest in participating (Appendix – Email to Breast Imaging Radiologists with Breast MRI Experience for Reader Study Participation). As this study results in no more than minimal risk to the participating radiologist and the imaging interpretation is within the scope of clinical practice where routine informed consent is not necessary, a verbal or written affirmation of their desire to participate in this study will serve as informed consent. Readers will not receive additional financial compensation for their participation and will not receive any specific credentials from training related to this reader study.

Prior to deidentified image interpretation, a Data Usage Agreement (DUA) will be executed for readers from institutions outside of BIDMC. Each reader will receive a reader ID, and all responses will be analyzed anonymously. Reader name, position, and experience reading breast imaging and breast MRI will be collected.

(iv) Reader imaging case interpretation: Prospectively acquired RSI and DCE-MRI+DWI images will be reviewed by each reader independently in two separate two-day sessions held at BIDMC, with each session separated by a one-month wash-out period, although some readers may require a third day: (i) RSI session and (ii) Ab-MRI and DCE-MRI+DWI session. T2- and T1-weighted pre-contrast images will be provided with the RSI images. Ab-MRI images will always be interpreted prior to interpreting the full DCE-MRI+DWI images. The order of the reader image interpretation will be randomized without replacement with the first

half of the readers (n=8) completing the RSI session first and the remaining readers (n=7) completing the Ab-MRI and DCE-MRI+DWI session first. The order of case presentation will also be randomized and counterbalanced within each group to minimize the effects of learning and/or fatigue. Readers will be blinded to the patient history, prior exams, and any biopsy result. All images in the reader study will be deidentified prior to presentation to the readers. All cases will be accessible via a BIDMC PACS workstation, which will be password protected with a separate log in for the readers. This separate log in will only provide access to the de-identified cases used in this study and no other studies on the BIDMC network.

The reader will document the location of every lesion in each RSI, Ab-MRI, and DCE-MRI+DWI case. RSI-CI and Z score maps will be calculated, as previously described for prostate.[30,34] There is no consensus yet as to what is a suspicious RSI Z score. We will train the 15 radiologist readers with cases with non-cancer and cancer cases with a range of RSI Z scores. The readers will be provided the RSI-CI Z score maps during the reader study and they will be allowed to interpret the study based on their training, the RSI-CI and Z score maps provided, and their judgment of malignancy. Each concerning lesion will be scored using the BI-RADS (Breast Imaging Reporting and Data System) score for screening based on the most suspicious finding; *i.e.,* 0, 1, or 2. The reader will need to provide a forced BI-RADS score for all cases receiving a BI-RADS score of 0; *i.e.,* 1, 2, 3, 4a, 4b, 4c, or 5. For the purposes of statistical analysis, to achieve a binary result, reader BI-RADS imaging scores of 1, 2, and 3 will be coded as negative/non-cancer and BI-RADS scores of 4 and 5 will be coded as positive/cancer, as per prior similarly designed studies. All data will be entered into the REDCap database system that only the principal investigator and co-investigators will have access to.

Limitations: Our study enrichment strategy means that we will not be drawing our cases from a true screening population, *i.e.,* women who are usually screened by MRI. We are studying women who undergo screening for breast cancer and this reader study allows a first step to assess the clinical value of RSI for screening. Further, with this design, RSI cannot be the primary detection modality, but again, this study provides preliminary data relatively inexpensively. Another potential concern is loss to follow-up, but we will avoid that issue by selecting only cases with confirmed benign or malignant status for use in the reader study.

DATA COLLECTION PROCEDURES

Images for the reader study will be sent and stored on the clinical PACS/RIS for viewing at the PACS workstation. These images will be deidentified prior to presentation to readers in the reader study. Readers will receive a separate log-in password that only provides them access to the specific de-identified cases used in this study on their PACS workstations.

Clinical information obtained from the OMR, biopsy results, routine BIDMC pre-imaging questionnaire, and data from the radiologist reader study will be collected and stored using the REDCap system (http://www.bidmc.org/Research/Core-Facilities/REDCap-EDC.aspx), only accessible to the principal investigator and designated co-investigators.

STATISTICAL PLAN

Statistical analysis: ROC curves will be created for the BI-RADS score, and the area under the [ROC] curve (AUC) will be calculated for each reader and each imaging set. The average

AUC will be calculated for RSI and for DCE-MRI+DWI. We will test the non-inferiority of RSI compared to DCE-MRI+DWI by establishing no loss of value in the average AUC with RSI compared to that of DCE-MRI+DWI. Testing the null hypothesis, H_o: $(AUC_{RSI} - AUC_{DCE}) \leq -0.06$, *versus* the alternative hypothesis, H_a:$(AUC_{RSI} - AUC_{DCE}) > -0.06$, will be based on a 95% confidence interval of the difference.

The ROC power and the sample size calculations are based on the methods of Zhou, Obuchowski and McClish.[50] 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 inter- observer variability is 0.002 and the intra-observer variability is 0.0004. The pooled readings from 15 readers on 40 cancer cases and 70 non-cancer cases will have at least 80% power to reject the null hypothesis that $(AUC_{RSI} - AUC_{DCE}) \leq -0.06$ with a 95% confidence interval on the difference, assuming the average AUCs for RSI and DCE-MRI+DWI are the same. The lower end of the confidence interval for the difference $(AUC_{RSI} - AUC_{DCE})$ must be greater than -0.06 to accept the alternative hypothesis of non-inferiority. **Table 2** shows the power analysis for reading sets with different cancer and non-cancer mix.

Table 2. Power analysis for reading sets with different cancer and non-cancer mix.

Number of cancers	Number of Non-cancers	Total N	Non-cancers/ cancers	Number of readers	Non-inferiority Margin	Power for Non-inferiority
40	70	110	1.75	15	0.06	0.802
40	80	120	2	15	0.06	0.811
40	90	130	2.25	15	0.06	0.818
40	100	140	2.5	15	0.06	0.823
40	70	110	1.75	14	0.06	0.783
40	80	120	2	14	0.06	0.792
40	90	130	2.25	14	0.06	0.799
40	100	140	2.5	14	0.06	0.805

Descriptive statistics will be used to evaluate patient responses to the survey.

REGULATORY REQUIREMENTS

This research project involves no more than minimal risk to the subjects enrolled in Group 1 who will be getting the usual breast MRI that all patients will get (RSI, as a type of DWI technique, will hereon be a part of the breast MRI exam at BIDMC for *all* patients). Therefore, we are requesting waiver of informed consent for this patient population. Cases will be retrieved after completion of all clinically required imaging necessary for inclusion in this study. For Group 2 subjects there is a moderate risk as there is an interventional procedure, an MRI being performed for study purposes only. Written, informed consent will be obtained by study staff from the 30 subjects to be enrolled into Group 2.

Participants will be receiving the standard DCE-MRI+DWI breast MRI and the study RSI. In general, unexpected findings during the *study* requiring further workup *will be handled in the same fashion* for which unexpected findings requiring further workup would be handled in routine clinical imaging.

Unexpected findings on DCE-MRI+DWI will be worked-up further as per routine clinical protocol. These additional lesions found on DCE-MRI+DWI but perhaps not seen on the regular mammogram, if suspicious, will require further work-up. Further work-up in routine clinical

breast imaging entails: biopsy and/or additional imaging, including mammography or ultrasound. The choice of whether to recommend biopsy and/or additional imaging will depend on the degree of suspicion of the interpreting radiologist. The radiologist or nurse practitioner/navigator will contact the patient's physician to discuss management, recommendations, and any alternatives, per routine clinical protocol for any concerning lesion. The physician will discuss recommendations and any alternatives with the patient. Scheduling of any further imaging or biopsy will be handled in conjunction with our radiology coordinators. Any additional imaging or biopsy will be billed to the patient's insurance. This is the same practice followed by our group anytime additional imaging or biopsy is recommended after a routine clinical breast MRI exam.

Unexpected findings on the study RSI is expected to be rare. These findings refer to findings identified on the study RSI later during the reader study that were not visible on the already interpreted standard breast MRI (current gold standard), prior mammogram or ultrasound. These additional lesions will be considered false positives for RSI and these patients will need at least 1-year clinical and/or imaging follow-up to confirm that it is indeed a false positive.

This proposed process of further evaluating lesions seen on the study RSI (*i.e.,* looking for a correlate on other standard breast MRI sequences and/or other imaging modalities) is identical to the process currently used to evaluate DWI sequences used in routine breast imaging clinical practice and is reasonable since RSI is a type of advanced DWI sequence. DWI is never used in isolation to make clinical decisions about patients. Therefore, if a lesion found on the study RSI (a type of advanced DWI) during the reader study has no concerning correlate on the standard breast MRI, it will be considered a false positive and no changes in clinical management will be made. We expect that RSI will increase the index of suspicion for already suspicious lesions found on standard breast MRI, and we will not use RSI to guide clinical management decisions or treatment. Only findings on the gold standard contrast-enhanced MRI will be used for clinical management.

The Principal Investigator, Dr. Vandana Dialani will be responsible for safety monitoring. Dr. Etta Pisano, who is a breast attending at BIDMC and has extensive experience designing and conducting radiologist reader studies, will be a co-investigator. Patient confidentiality will be protected according to HIPAA guidelines and no patient identifiable information will be released to outside institutions or out of the hospital.

Group 1: All patients presenting for their usual breast cancer screening MRI that meet the eligibility checklist criteria will be eligible. No additional screening beyond their completion of the BIDMC routine MRI safety screening questionnaire and Breast care center patient questionnaire will be performed.

Group 2: Identified potential subjects will be contacted by our Research Associate by telephone or in person at the time of their consultation after a callback diagnostic exam if a biopsy is to be recommended. The study team will only contact patients who have already been introduced to the study by the breast imaging specialist at the time of consult or the referring provider, or patients who initiate interest in the study by independently reading the study's patient flier available for all patients in the consult room (Appendix). Patients will be given information about the study through in person discussion and the patient flier with the option of participation. If patients meet eligibility criteria (using our eligibility checklist) and are willing to participate, they will be consented and enrolled as participants.
A suggested template of what the recruiter will say is detailed in the Appendix: Group 2 Recruitment Script. If the subject says that she wishes to hear more, the Research Associate

will explain the study in greater detail and answer the potential participant's questions.

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101. When required by REGIST-101, registration must occur prior to the initiation of protocol-specific procedures or assessments.

Registration requires a signed informed consent document and a completed eligibility checklist according to DF/HCC SOP REGIST-104.

Radiologist readers will be identified as consultants for their expertise in breast MRI imaging as defined by the ACR guidelines and contacted via email. A verbal or written response affirming their desire to participate in this study will satisfy the informed consent since this study results in no more than minimal risk to the participating radiologist and the imaging interpretation is within the scope of clinical practice where routine informed consent is not necessary. A waiver of documentation of consent has been requested for the reader study.

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