II. Research Plan

Project Title:

Abstract:

The current management strategy for mammographically suspicious breast calcifications, as laid out in the Breast Imaging-Reporting and Data System (BI-RADS) Atlas, does not incorporate patient specific risk factors and instead recommends biopsy for all calcifications with an unadjusted 2%-95% chance of malignancy. Furthermore, the evidence for these recommendations is sometimes based on relatively small sample sizes and classifies malignancy as everything from low grade ductal carcinoma *in situ* (DCIS) to high grade inflammatory carcinoma. While identifying invasive cancer at an early stage is the primary goal of screening mammography, aggressively pursuing low-grade DCIS or atypia may not be appropriate for all patients. With high false positive rates and overdiagnosis of clinically insignificant disease, we are exposing patients to needless morbidity and anxiety, while also driving up health care costs. A more personalized calcification management strategy would incorporate patient risk factors in order to allow radiologists to accurately predict the likelihood of specific breast pathologies, in order to offer more tailored management recommendations.

This proposal aims to provide the evidence to begin developing just such a management system. We plan to review the mammograms from approximately 3000 consecutive patients over the past 5 years who underwent directional vacuum-assisted biopsy for suspicious calcifications. BI-RADS imaging features will be identified by fellowship trained breast radiologists. Detailed patient information including age, menopausal status, race/ethnicity, and Gail score will be collected from the medical record. All biopsy specimens will be reviewed to collect lesion pathology and when appropriate and available tumor grade, hormone receptor status, Ki67 status, and Recurrence Score. Outcomes based analysis for specific breast pathologies will be performed according to imaging features in the context of detailed patient demographic information and risk factors. This information will be used to develop a personalized evidence based algorithm for the management of suspicious mammographic calcifications.

Specific Aims

The principal objective of this project is to develop a personalized evidence based algorithm for the management of suspicious breast calcifications detected on routine screening mammography.

We hypothesize that mammography BI-RADS imaging features in conjunction with detailed patient demographic information and risk factors can be used to personalize the clinical management of calcifications.

If radiologists can more accurately predict specific breast pathology at the time of the initial diagnostic workup, this could allow personalized decision making for patients which may:

- Reduce the number of benign needle biopsies (false positives)
- Reduce the number of biopsies for clinically insignificant disease (overdiagnosis)
- Decrease unnecessary patient morbidity and anxiety
- Decrease health care costs

Specific Aim 1: Identify the distribution of specific breast pathologies for BI-RADS calcification descriptors.

Hypothesis: Mammography BI-RADS calcification descriptors differ between specific breast pathologies (e.g., ADH, low grade DCIS, high grade IDC).

Specific Aim 2: Apply patient demographic information and risk factors to BI-RADS calcification descriptors to predict specific breast pathologies.

Hypothesis: The predictive power of BI-RADS calcification descriptors will be significantly increased when applied in the context of patient personal risk factors and demographic information.

Specific Aim 3: Develop a personalized evidence based algorithm for the management of suspicious calcifications that incorporates imaging features and individualized patient information.

Hypothesis: An evidence based algorithm can be created that includes breast calcification imaging features and detailed patient information to accurately predict breast pathology in order to guide clinical decision making and tailor management recommendations.

Significance, Innovation, and Relationship to Health Services Research

The BI-RADS Atlas provides guidelines for the management of breast calcifications with final assessment categories that correspond with the likelihood of malignancy: category 3 (0-2%), 4A (>2%–≤10%), 4B (>10%–≤50%), 4C (>50%–95%), and 5 (>95%) [1]. However, this segmentation does not appreciably change initial clinical management as all calcifications with a greater than 2% likelihood of malignancy are recommended for biopsy. Furthermore, this risk stratification does not take into account patient factors (e.g., age, menopausal status, lifetime risk of breast cancer) or local environmental factors (e.g., breast density) when calculating the likelihood of malignancy. While excluding these factors creates a very straightforward management algorithm, it likely exposes many patients to unnecessary biopsies (i.e., false positive) which increase patient morbidity and anxiety, while driving up health care costs [2,3]. With 18 million US women undergoing screening mammography annually and a 10% false-positive rate this leads to roughly $1 billion in unnecessary health care spending, largely due to biopsy costs [4-7]. Instead of applying a "one size fits all" management strategy for calcifications, an approach that incorporates both imaging features and patient information would allow personalized management. In an era of precision medicine, the radiologist can play a central role in the management strategy of calcifications, but data are needed upon which to base this approach.

The first step towards developing a personalized management strategy for calcifications is to have a very accurate assessment of the likelihood of malignancy for specific imaging descriptors, since calcification morphology is likely to be the greatest predictor of disease. However the available evidence, as referenced in the BI-RADS Atlas, is drawn from studies that are limited by the use of old screen film technique, smaller sample sizes, single reader assessment of morphology, or selection bias [8-11]. This is especially apparent for the coarse heterogeneous descriptor, first introduced in 2003 as part of the 4th edition BI-RADS Atlas [12], which has been reported to have a 13% average likelihood of malignancy based on two studies with a total sample size of 24 [8,10]. Modern studies which utilize digital mammography, large sample sizes, and multiple readers to compensate for interobserver variability are currently lacking.

The next step towards personalizing management is to have a detailed assessment of specific pathology outcomes for imaging features. Prior work used to establish rates of malignancy for imaging descriptors has lumped low grade ductal carcinoma *in situ* (DCIS) through high grade invasive ductal carcinoma (IDC) into the same category of "malignancy" [8-11]. This classification has not kept pace with our growing understanding of tumor biology. Similar to changes in the thought process regarding prostate cancer outcomes [13], there is an emerging belief that low grade DCIS may not be as clinically significant as previously thought, which has sparked a debate regarding overdiagnosis and whether the word carcinoma should even be included in the name DCIS [14-19]. As a result, the outcome measures utilized in subsequent studies need to be more nuanced in order to distinguish between clinically meaningful and clinically insignificant disease (i.e, overdiagnosed disease). For example, in the actively enrolling Tomosynthesis: Comparison of Full-Field Digital Mammography With Digital Breast Tomosynthesis Trial (TMIST), the primary outcomes are patients with stage II or higher disease as well as tumors over 6 mm with aggressive markers [20]. This is a departure from the prior

Digital Mammographic Imaging Screening Trial (DMIST) which utilized all cases of DCIS and IDC as the primary outcome [21].

For overdiagnosed disease, which would likely include atypia and low grade DCIS, there is a growing interest in decreasing the number of biopsies and surgical excisions and instead following patients with active surveillance imaging protocols [16,22,23]. The safety and effectiveness of an active surveillance program has been identified as a key research need by the Patient-Centered Outcomes Research Institute [24] and the National Institutes of Health Panel on the Diagnosis and Management of Ductal Carcinoma *in Situ* [25]. However, in order for an active surveillance imaging program to be successful, radiologists must be able to accurately predict the likelihood of clinically meaningful disease. Previous efforts to predict invasive disease on surgical excision after atypia or DCIS was identified from a needle biopsy have been limited in only looking at gross lesion size, the presence of concomitant masses, or number of foci [26-28]. If imaging features in conjunction with patient risk factors can provide a detailed assessment of the likelihood of clinically significant disease, then patients with a low risk may instead choose to undergo active surveillance.

The BI-RADS Atlas provides a very straightforward and conservative management approach for calcifications seen on mammography. However, in order to help suppress high false positive rates and overdiagnosis, it may be helpful to employ a more personalized management approach. On a case by case basis, patients who have been counseled regarding their personal risk of clinically significant disease may feel that the increased morbidity, anxiety, and health care costs of a biopsy may outweigh the benefits of proving clinically insignificant disease. However, if there is to be a transformative shift in the approach to the management of calcifications then larger studies using modern imaging techniques with detailed assessments of pathology outcomes and patient risk factors are needed. Such data would allow radiologists to take an active role in helping to identify clinically relevant disease. This proposal aims to be a step in that direction.

Progress Reports of Previous/Preliminary Research

The spectrum of breast pathology differs with patient age, but there is little published work comparing differences in the distribution of imaging features with pathology outcomes for various age groups [29-31]. To investigate the association between calcification morphology and breast pathology in elderly women, we performed a pilot study on women over the age of 70 who underwent stereotactic biopsy for suspicious calcifications. The mammograms from 176 consecutive patients from 2011-2014 were reviewed by three fellowship trained breast radiologists who reported the calcification morphology according to the BI-RADS lexicon. Consensus morphology descriptors were obtained and compared to the most clinically significant final pathology results from the stereotactic and/or surgical biopsy.

The initial results are shown in Table 1 with a specific breakdown of pathology outcomes by calcification morphology. For comparison, the last column includes the rates of malignancy cited in the BI-RADS Atlas, which refers to DCIS plus IDC.

	Pilot study pathology outcomes				**"Malignancy" rates cited in BI-RADS Atlas**
Morphology	**Benign, n (%)**	**Atypical, n (%)**	**DCIS, n (%)**	**IDC, n (%)**	
Amorphous (n=31)	**16 (52)**	**7 (23)**	**7 (23)**	**1 (3)**	**21%**
Coarse hetero (n=35)	**31 (88)**	**3 (9)**	**1 (3)**	**0 (0)**	**13%**
Fine pleomorphic (n=88)	**39 (44)**	**7 (8)**	**33 (38)**	**9 (10)**	**29%**
Fine linear or fine-linear branching (n=22)	**5 (23)**	**6 (27)**	**8 (36)**	**3 (14)**	**70%**

Table 1. Pathology outcomes as a function of BI-RADS calcification morphology with reference malignancy rates from the BI-RADS Atlas [1].

The results demonstrate that for the coarse heterogeneous morphology descriptor the rate of malignancy is much lower in the over age 70 population (3% DCIS and 0% IDC) than in the BI-RADS reference population (13% DCIS plus IDC). Furthermore, the 3% malignancy rate in the study sample is very close to the 2% threshold currently used to recommend biopsy and consists only of cases of DCIS. The pilot study data is only from a sample set of 35, which exceeds the 24 patients reported in the BI-RADS Atlas. These results will need to be explored further, but the preliminary work is encouraging that there are differences in pathology outcomes for calcification morphology between the general patient population and the population over age 70.

Experimental Design and Methods

Specific Aim 1: Identify the distribution of specific breast pathologies for BI-RADS calcification descriptors.

Initial Case Selection

Patients who underwent directional vacuum-assisted biopsy (DVAB) over the past five years will be identified via a search through the Duke Enterprise Data Unified Content Explorer (DEDUCE) system [32]. The DEDUCE system allows all radiology and pathology reports to be searched for current procedural terminology (CPT) codes as well as specific text strings. The CPT code 19103, which refers to percutaneous vacuum-assisted biopsy using image guidance, and the CPT code 19081, which replaced CPT code 19103 starting in 2014, will be searched from 2010-2014 to identify all patients who underwent DVAB. This time interval was chosen to ensure that all patients underwent initial imaging with digital mammography, rather than older screen film technology. The Breast Imaging Division at Duke University Medical Center performs approximately 600-700 DVAB per year. Our breast imaging team consists of all fellowship trained breast radiologists and strict adherence to the BI-RADS recommendations for the biopsy of suspicious calcifications (BI-RADS 4 and 5) is our standard of care. All DVAB at our institution are performed with 9 gauge biopsy needles with at least 6-12 samples obtained per site.

The list of consecutive cases will be filtered to include only patients who were biopsied for calcifications (a minority of patients undergo DVAB for asymmetries or small masses that are not seen on ultrasound). Specimen radiographs will be reviewed in all cases to confirm that the suspicious calcifications were successfully biopsied. The radiology reports will also be reviewed to ensure there was radiologic-pathologic concordance for all biopsies. Our practice is to amend all radiology reports if there is discordance between the imaging findings and the biopsy results. This final pool of approximately 3000 cases (600 cases per year after exclusions for 5 years) will represent the initial study pool.

Image Review

Fellowship trained faculty from the Division of Breast Imaging who are dedicated breast radiologists will serve as readers for the study. All faculty have dedicated research time available for assistance with the execution of this project. All readers will be blinded to the pathology results. The initial diagnostic digital mammograms, including spot magnification views, will be viewed on existing 5 MP high resolution clinical monitors certified by the Mammography Quality Standards Act (MQSA) for viewing mammographic studies. Cases will be excluded if there are suspicious features which would prompt a biopsy irrespective of the calcifications (e.g., masses, associated architectural distortion). Consensus interpretations will be generated of the calcification morphology and distribution, as well as breast composition according to the 5th edition BI-RADS lexicon [1]. Consensus interpretations will be used to compensate for interobserver variability. The long axis extent of calcification distribution will be measured. All images will be correlated with subsequent post-biopsy mammograms to confirm that the imaging descriptors refer to the appropriate biopsy sites.

Pathology Results

All breast pathology samples at our institution are reviewed by fellowship trained pathologists specializing in breast pathology within the Department of Pathology. The pathology reports will be reviewed from the initial breast biopsy. The most clinically significant pathologies (e.g., ADH < DCIS < IDC) will be recorded. The standard of care at our institution is for all atypical lesions, *in situ* disease, and invasive disease to undergo surgical excision. Information from both the initial breast biopsy and subsequent surgical excision, when appropriate, will be recorded. For cases of *in situ* and invasive disease, additional information regarding tumor grade, hormone receptor status, Ki67, and 21 gene Recurrence Score will be reported when available. Surrogate molecular subtypes for all cases of invasive disease will be calculated (luminal A: ER/PR+, HER2-; luminal B: ER/PR+, HER2 +; HER2: ER-, PR-, HER2+; basal: ER-, PR-, HER2-) [33].

Data Analysis

The distribution of final breast pathology will be tabulated for each imaging descriptor with confidence intervals calculated. Within individual breast pathologies, we will segment out additional pathology variables. Specifically, the incidence of low, intermediate, and high tumor grade for cases of *in situ* and invasive disease will be calculated. For cases of invasive disease, we will provide the distribution of surrogate molecular subtypes, as well as Ki67 status, and Recurrence Score when available. This will allow the generation of very detailed tables of pathology outcomes. Since our sample sizes will be relatively large, we will be able to produce relatively narrow confidence intervals. Theoretical 95% confidence intervals for varying sample sizes and observed proportions are shown in Table 2.

Sample Size	Outcome	95% CI
250	**2%**	**±1.74**
250	**5%**	**±2.70**
250	**10%**	**±3.72**
500	**2%**	**±1.23**
500	**5%**	**±1.91**
500	**10%**	**±2.63**
1000	**2%**	**±0.87**
1000	**5%**	**±1.35**
1000	**10%**	**±1.86**

Table 2. 95% confidence intervals for different sample sizes and theoretical outcomes.

The Duke Office of Information Technology provides software for data analysis, including Microsoft Excel and SAS, free of charge. Computers already purchased through educational funds are available for use.

Future Directions and Potential Implications

This information will allow radiologists to more accurately predict the likelihood of specific breast pathologies based on BI-RADS calcification descriptors and thus afford them the opportunity to have more detailed discussions with patients about outcomes. If specific imaging features (e.g., coarse heterogeneous morphology) are associated with a very low likelihood of malignancy, and in particular invasive disease, then these findings may influence recommendations in future editions of the BI-RADS Atlas.

Specific Aim 2: Apply patient demographic information and risk factors to BI-RADS calcification descriptors to predict specific breast pathologies.

The cases, pathology results, and imaging features identified by consensus expert breast radiologist interpretation will be carried over from Aim 1.

Patient Information

Patient demographic information will be collected from a review of the medical records. Age, self-reported race/ethnicity, and menopausal status will be recorded. When sufficient information is available (e.g., personal history of breast cancer, BRCA, age at first menstrual period, family history, prior breast biopsies) the patient's Gail score will be calculated or recorded from the provider notes [34].

Data Analysis

Analysis will be performed among all cases with a specific breast calcification descriptor (e.g., all cases with amorphous morphology). A multivariable logistic regression model will be performed to test associations between patient and breast descriptors with final pathology outcomes. The input variables will be patient age, race/ethnicity (Caucasian or non-Caucasian), menopausal status (pre-menopausal/peri-menopausal or post-menopausal), calcification long axis length, and breast density (fatty/scattered fibroglandular or heterogeneously dense/extremely dense). Subgroup analysis will be performed with the Gail score as an input variable when available. The analysis will be performed for three separate dichotomous outcome variables, which are chosen to represent a range of conservative and aggressive potential management strategies:

1. all atypical disease and cancer (*in situ* and invasive) versus benign disease
2. all cancer (*in situ* and invasive) versus all else
3. high grade cancer (*in situ* and invasive) versus all else

A feature reduction step will be performed to exclude features that are highly associated with one another and to exclude variables which have minimal effect on the model. Minimum sample size calculations based on the projected outcomes (i.e., percentage of cases with cancer) and the number of covariates are shown in Table 3 per the Peduzzi et al method [35]. The total study population of approximately 3000 will be distributed among the calcifications descriptors (n=4), but assuming a roughly even distribution between descriptors (3000/4=750) and the exclusion of at least one covariate (5-1=4), we should be able to detect significant associations near the 5% level and perhaps lower if individual descriptors are better represented or if more covariates are excluded.

		Number of covariates			
		2	**3**	**4**	**5**
Outcome	**2%**	**1000**	**1500**	**2000**	**2500**
	5%	**400**	**600**	**800**	**1000**
	10%	**200**	**300**	**400**	**500**
	20%	**100**	**150**	**200**	**250**
	50%	**4**	**60**	**80**	**100**

Table 3. Theoretical sample size calculations for outcomes and covariates

The Department of Radiology has PhD level biostatisticians on staff available for assistance regarding data analysis and modeling.

Future Directions and Potential Implications

The influence of imaging features and patient information on specific pathology outcomes may guide future work on overdiagnosis. If different thresholds are set for clinically significant disease, then the recommendation to biopsy certain calcification morphologies may change when applied in the setting of patient specific risk factors.

Specific Aim 3: Develop a personalized evidence based algorithm for the management of suspicious calcifications that incorporates imaging features and individualized patient information.

The likelihood of malignancy for specific calcification imaging descriptors identified in Aim 1 and the significant covariates identified in Aim 2 will be used to develop a decision tree algorithm for the management of calcifications.

Creation of the decision tree

The root of the tree will be a specific calcification descriptor (e.g., amorphous, coarse heterogenous) so as to provide a clinically relevant reference point for radiologists. The branches will then be derived from the covariates identified in Aim 2 (e.g., age, race/ethnicity). The final endpoint of each branch will be the outcomes described in Aim 2 (e.g., percentage of cases with high grade cancer). A theoretical algorithm is shown in Figure 1. The model can be adjusted through the continuous variables (age and calcification long axis length) and via changes to the categorization of the ordinal variables (e.g., breast density). These adjustments will allow the calculation of different outcome percentages.

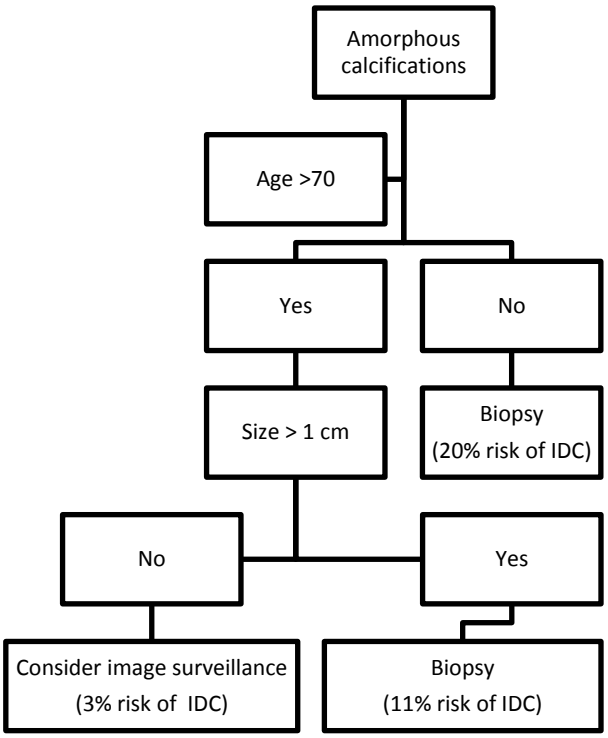

Figure 1. Theoretical algorithm for the management of amorphous calcifications

Future Directions and Potential Implications

This research proposal and the development of the decision tree algorithm will provide evidence to justify testing multiple additional hypotheses in a prospective fashion.

1. Patients with calcifications previously deemed suspicious but with a low risk of clinically significant disease may choose to avoid initial biopsy and instead pursue imaging surveillance until there are new imaging features to suggest invasive disease.
2. Patients with biopsy proven atypia or low grade *in situ* disease but no imaging features to suggest invasive disease may be enrolled in an active surveillance program and followed with imaging instead of immediate surgical excision which is the current standard of care.

In addition, the decision tree algorithm can be adjusted to calculate different outcome percentages which can be helpful in assessing the implications (e.g., false positives, overdiagnosis) of changing the 2% likelihood of malignancy threshold for recommending biopsy.

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