Can Breast Cancer Molecular Subtype Help to Select Patients for Preoperative MR Imaging?[1]

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Purpose: To assess whether breast cancer molecular subtype classified by surrogate markers can be used to predict the extent of clinically relevant disease with preoperative breast magnetic resonance (MR) imaging.

Materials and Methods: In this HIPAA-compliant, institutional review board–approved study, informed consent was waived. Preoperative breast MR imaging reports from 441 patients were reviewed for multicentric and/or multifocal disease, lymph node involvement, skin and/or nipple invasion, chest wall and/or pectoralis muscle invasion, or contralateral disease. Pathologic reports were reviewed to confirm the MR imaging findings and for hormone receptors (estrogen and progesterone subtypes), human epidermal growth factor receptor type 2 (HER2 subtype), tumor size, and tumor grade. Surrogates were used to categorize tumors by molecular subtype: hormone receptor positive and HER2 negative (luminal A subtype); hormone receptor positive and HER2 positive (luminal B subtype); hormone receptor negative and HER2 positive (HER2 subtype); hormone receptor negative and HER2 negative (basal subtype). All patients included in the study had a histologic correlation with MR imaging findings or they were excluded. χ^2 analysis was used to compare differences between subtypes, with multivariate logistic regression analysis used to assess for variable independence.

Results: Identified were 289 (65.5%) luminal A, 45 (10.2%) luminal B, 26 (5.9%) HER2, and 81 (18.4%) basal subtypes. Among subtypes, significant differences were found in the frequency of multicentric and/or multifocal disease (luminal A, 27.3% [79 of 289]; luminal B, 53.3% [24 of 45]; HER2, 65.4% [17 of 26]; basal, 27.2% [22 of 81]; $P < .001$) and lymph node involvement (luminal A, 17.3% [50 of 289]; luminal B, 35.6% [26 of 45]; HER2, 34.6% [nine of 26]; basal 24.7% [20 of 81]; $P = .014$). Multivariate analysis showed that molecular subtype was independently predictive of multifocal and/or multicentric disease.

Conclusion: Preoperative breast MR imaging is significantly more likely to help detect multifocal and/or multicentric disease and lymph node involvement in luminal B and HER2 molecular subtype breast cancers. Molecular subtype may help to select patients for preoperative breast MR imaging.

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Routine use of magnetic resonance (MR) imaging to preoperatively evaluate patients with breast cancer who may qualify for breast conservation therapy engenders controversy among breast cancer care providers (1,2). Compared with diagnostic mammographic and ultrasonographic imaging, breast MR imaging helps to measure tumor size more accurately and helps to detect multifocal, multicentric, and contralateral disease, all of which may change treatment planning (3,4). Despite these advantages, the widespread use of preoperative breast MR imaging has not been shown to confer survival benefits, and some reports suggest that it may lead to worse patient outcomes (1,2,5–7). This evidence suggests that breast MR imaging is a powerful tool, but its use may need to be refined and directed to a patient population in whom the risk-to-benefit ratio can be optimized. To date, there is a lack of results from prospective, randomized controlled trials that evaluate the effect of preoperative breast MR imaging on treatment planning and long-term patient outcomes.

Although breast cancer was initially considered a single-disease process, recognition of the heterogeneity of this disease led to the differentiation of breast carcinoma into distinct molecular subtypes on the basis of gene expression profiling (8,9). Distinct molecular subtypes respond differently to therapy (10–12) and confer different prognoses (13). Although this area of research is evolving, the current commonly accepted molecular subtypes include luminal A, luminal B, human epidermal growth factor receptor type 2 (HER2), and basal types (14). Luminal A is generally the most common molecular subtype and typically confers the best prognosis (14). Luminal B subtype has a good response to radiation therapy and intermediate survival (15), while HER2 and basal subtypes show good response to chemotherapy but have the worst overall survival (11). These subtypes correlate with combinations of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, which have been used as surrogate markers to determine molecular subtype in place of more expensive and time-consuming complete transcriptome analysis (16–19). ER, PR, and HER2 tests that define these surrogates are routinely performed on core biopsy specimens of breast cancer by using immunohistochemical and fluorescence in situ hybridization analysis, and they are typically available to providers before the decision to pursue preoperative breast MR imaging is made.

The relationship between MR imaging and breast cancer molecular subtypes is an emerging area of research. The available published literature focused almost exclusively on the use of MR imaging to evaluate how different molecular subtypes respond to neoadjuvant chemotherapy (18,20–23). Although data from pathologic analyses in literature show that the distribution of disease on mastectomy specimens varies by molecular subtype (24), to our knowledge, there are no studies that demonstrate whether these differences are distinguishable on preoperative breast MR imaging. Because breast cancer molecular subtypes respond differently to therapeutic interventions and because differences in local and regional disease help to guide treatment planning, the objective of our study is to assess whether breast cancer molecular subtype classified by surrogate markers can be used to predict the extent of clinically relevant disease with preoperative breast MR imaging. Targeted use of preoperative breast MR imaging in patients with specific molecular subtypes may allow for more cost-effective and clinically efficacious care.

Advances in Knowledge

- By using preoperative breast MR imaging, multifocal or multicentric disease was reported significantly more often in luminal B (53.3%) and human epidermal growth factor receptor type 2 (HER2; 65.4%) molecular subtype breast cancers compared with luminal A (27.3%) or basal (27.2%) subtypes ($P < .001$).
- By using preoperative breast MR imaging, metastatic lymph node involvement was reported significantly more often in luminal B (35.6%) and HER2 (34.6%) molecular subtype breast cancers compared with luminal A (17.3%) or basal (24.7%) subtypes ($P = .014$).

Implication for Patient Care

- Knowledge of higher pretest probability for identification of multifocal or multicentric disease and/or lymph node involvement in luminal B and HER2 molecular subtype breast cancers may help direct the use of preoperative breast MR imaging.

Materials and Methods

Patient Inclusion and Exclusion Criteria

The local institutional review board approved this retrospective and Health Insurance Portability and Accountability Act–compliant study. Informed consent was waived. We retrospectively reviewed clinical interpretation reports from consecutive preoperative breast MR examinations in 601 patients over a 3-year period from July 2006 through June 2009. Patients with a remote history of breast cancer (ie, patients who

Published online before print
10.1148/radiol.14140594 **Content codes:** BR MR

Radiology 2015; 274:352–358

Abbreviations:
ER = estrogen receptor
HER2 = human epidermal growth factor receptor type 2
PR = progesterone receptor

Author contributions:
Guarantors of integrity of entire study, L.J.G., K.S.J.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, L.J.G., K.S.J., P.K.M., J.A.B.; clinical studies, L.J.G., K.S.J., P.K.M., J.A.B.; experimental studies, J.A.B.; statistical analysis, L.J.G.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

underwent previous definitive therapy; n = 29) or elective breast surgery (eg, implants or mammoplasty; n = 20) and those who were undergoing breast cancer treatment (eg, chemotherapy or radiation therapy) at the time of the study (n = 55) were excluded. Additionally, patients who had MR findings without histopathologic correlation or patients with missing receptor status data were excluded (n = 56). Therefore, there were 441 patients with preoperative breast MR imaging reports available for analysis.

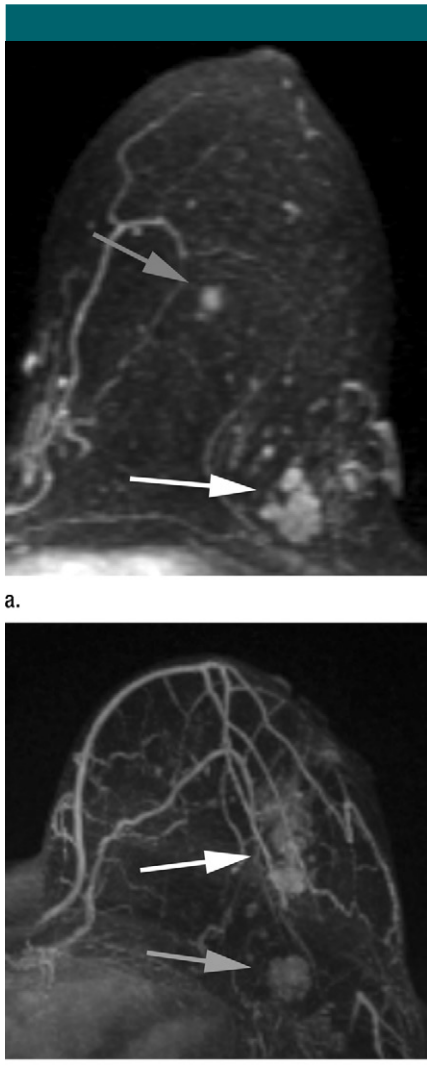
Imaging Protocol

All breast MR examinations were performed with a 1.5-T imager (Signa HDx and Signa HDxt, GE Healthcare, Little Chalfont, United Kingdom; Magnetom Avanto, Siemens, Munich, Germany; 46, five, and 78 patients, respectively) or a 3-T imager (Signa HDx and Signa Excite, GE Healthcare; Magnetom Trio, Siemens; 231, 30, and 51 patients, respectively) in the prone position with a dedicated seven-channel breast coil (Invivo, Orlando, Fla). Each study included a precontrast nonfat-saturated T1-weighted sequence and a precontrast fat-saturated T2-weighted sequence. In addition, a precontrast fat-saturated gradient-echo T1-weighted sequence was performed, followed by three or four dynamic postcontrast T1-weighted gradient-echo series images with fat suppression after intravenous administration of gadopentetate dimeglumine (Magnevist; Bayer Health Care, Berlin, Germany) or gadobenate dimeglumine (MultiHance; Bracco, Milan, Italy) by using a weight-based dosing protocol. All imaging was reconstructed in the axial plane, and subtraction and maximal intensity projection sequences were generated.

Data Collection

The MR images were reviewed for descriptions of multicentric or multifocal disease, lymph node involvement, skin or nipple invasion, chest wall or pectoralis muscle invasion, and contralateral disease with no new interpretations made. Multifocal disease was defined as findings within the same breast quadrant suspicious for additional sites of malignancy; multicentric disease was defined as findings suspicious for additional sites of malignancy within different quadrants of the ipsilateral breast; and contralateral disease was defined as suspicious findings in the opposite breast. MR findings that were suggestive of lymph node involvement included abnormal morphologic findings and/or increased cortical thickness that resulted in Breast Imaging Reporting and Data System final assessment scores of 4 (suspicious) or 5 (highly suggestive of malignancy). Cases where skin or nipple invasion was suspected were recorded if the report described skin or nipple enhancement to indicate skin invasion. Chest wall or pectoralis muscle invasion was considered positive if the report described abnormal enhancement in these locations indicating invasion. There were no new interpretations, and only original MR examinations that matched the previously mentioned descriptors were considered positive.

All reported findings detected by using MR imaging that were considered suspicious were correlated with pathologic reports from subsequent core-needle, skin-punch, or surgical biopsies, as appropriate. For example, if the MR report described a lymph node that was considered suspicious with abnormal morphologic analysis, then the pathologic report from the corresponding core-needle lymph node biopsy or surgical lymph node dissection was reviewed to confirm or deny the presence of cancer in the lymph node. In all cases, the description of the lesion from the MR report was correlated with either the corresponding image–guided core biopsy or surgical pathologic reports to ensure that the findings described by using MR imaging had histopathologic validation. Patients were excluded from analysis if suspicious abnormal findings described by using their MR examinations did not have correlative histopathologic confirmation. The Figure shows examples of multifocal disease and lymph node involvement in a case of luminal B (Fig a) and HER2 (Fig b) molecular subtype breast cancer. Tumor size was collected from the MR imaging report on the basis of the largest dimension provided. In cases of excisional biopsy where no residual tumor was observed by using subsequent MR imaging, the measurement from the pathologic analysis of the initial specimen was used (n = 91).



a.

b.

Maximum intensity projection breast MR images. **(a)** A luminal b molecular subtype breast cancer (white arrow) is seen with a small satellite lesion (gray arrow). **(b)** A HER2 molecular subtype breast cancer (white arrow) is seen with a metastatic axillary lymph node (gray arrow).

ER, PR, and HER2 status were determined by using the pathologic reports obtained from the initial breast

Table 1

Classification of Surrogate Molecular Subtypes by Receptor Status

Subtype	Receptor Status
Luminal A	ER positive and/or PR positive, HER2 negative
Luminal B	ER positive and/or PR positive, HER2 positive
HER2	ER negative and PR negative, HER2 positive
Basal	ER negative, PR negative, and HER2 negative

biopsy. ER and PR status were considered positive if the Allred score from the immunohistochemical stain was greater than or equal to 3. HER2 status was considered positive if the immunohistochemical stain was 3+, or 2+ with confirmation of HER2 gene amplification by fluorescence in situ hybridization (PathVysion HER2 DNA Probe Kit; Abbott Laboratories, Chicago, Ill) (25,26). By using the pathologic report, the Nottingham tumor grade was recorded as low, intermediate, or high on the basis of a calculation of the tubule formation, nuclear grade, and mitotic count (27).

Data Analysis

Breast cancers were categorized into molecular subtypes on the basis of the ER, PR, and HER2 markers, which were defined by previous investigators (17,18). Surrogate molecular subtypes were classified on the basis of the ER, PR, and HER2 status (Table 1). Patient and tumor characteristics were compared between molecular subtypes by using χ^2 analysis or analysis of variance for proportions and means, respectively.

Biopsy-confirmed multicentric and multifocal disease, skin and nipple involvement, chest wall and pectoralis muscle invasion, and low and intermediate tumor grade were paired for analysis. We compared the proportions of multicentric or multifocal disease, lymph node involvement, skin or nipple invasion, chest wall or pectoralis muscle invasion, and contralateral disease between molecular subtypes by using χ^2 analysis. Multivariate logistic regression analysis was used to determine whether molecular subtype was independently predictive of lymph node involvement and multifocal or multicentric disease after controlling for age (continuous), tumor size (continuous), and nuclear grade (low or intermediate vs high). Luminal A was used as the reference group. Patients with missing tumor size or grade were excluded from the multivariate analysis (n = 11). Statistical analysis was performed by using statistical software (JMP Pro version 9.0.0; SAS Institute, Cary, NC). A P value less than .05 indicated statistical significance. All statistical tests were two sided.

Results

In 441 patients, the average age was 52.2 years ± 11.2 (standard deviation). The average tumor size was 25.2 mm ± 17.4, and the tumor measurements from MR imaging (27.3 mm ± 17.8) were greater than those from the pathologic reports (17.1 mm ± 12.8; $P <$ .001). We graded the tumors as follows: 22.0% (97 of 441), low grade; 49.7% (219 of 441), intermediate grade; and 28.3% (125 of 441), high grade. Breast cancers in the 441 patients were classified into molecular subtypes as follows: 289 (65.5%), luminal A; 45 (10.2%), luminal B; 26 (5.9%), HER2; and 81 (18.4%), basal. The patient and tumor characteristics per molecular subtype are shown in Table 2.

Multicentric or multifocal disease was nearly identical in frequency in luminal A (27.3% [79 of 142]) and basal (27.2% [22 of 81]) subtype malignancies. However, multicentric or multifocal disease was reported significantly more frequently ($P <$ .001) by using MR imaging in luminal B (53.3% [24 of 45]) and HER2 (65.4% [17 of 26]) subtypes. Lymph node involvement was significantly (P = .014) more commonly reported in luminal B (35.6% [16 of 45]) and HER2 (34.6% [nine of 26]) subtypes than luminal A (17.3% [50 of 289]) or basal (24.7% [20 of 81]) subtypes. There was no significant difference between breast cancer subtypes in the distribution of skin or nipple invasion (P = .203), chest wall or pectoralis muscle invasion (P = .396), or contralateral disease (P = .375). The distribution of MR imaging findings by molecular subtype is shown in Table 3. There was no significant difference in the distribution of MR imaging findings between patients imaged with 1.5-T or 3-T imagers for multifocal or multicentric disease (P = .74), contralateral disease (P = .99), lymph node involvement (P = .28), skin or nipple invasion (P = .73), and pectoralis muscle or skin invasion (P = .50).

At multivariate analysis, after controlling for tumor size, patient age, and tumor grade, molecular subtype was an independent predictor of multifocal or multicentric disease ($P <$ .001). Patients with luminal B subtype cancer were 2.8 times more likely than those with luminal A subtype cancer to have multifocal or multicentric disease (odds ratio, 2.8 [95% confidence interval: 1.4, 5.4]). Patients with HER2 subtype cancer were 4.1 times more likely to have multifocal or multicentric disease than those with luminal A subtype cancer (odds ratio, 4.1 [95% confidence interval: 1.7, 10.4]). Molecular subtype was not found to be independently predictive of lymph node involvement on multivariate analysis (P = .224). The results of the multivariate logistic regression analysis are shown in Table 4.

Discussion

The incorporation of breast cancer molecular subtype information into clinical breast cancer treatment planning is an important step toward personalized medical care. Breast cancers with different molecular subtypes have different patterns of initial disease presentation (24) and metastatic spread (10) and respond differently to radiation therapy (15,28) and chemotherapy (12,29). These findings suggest that diagnostic work-up, treatment strategies, and surveillance monitoring may be better guided by information garnered

Table 2

Patient and Tumor Characteristics according to Surrogate Molecular Subtype

Parameter	All Subtypes	Surrogate Molecular Subtype				*P* Value
		Luminal A	Luminal B	HER2	Basal	
No. of patients	441	289 (65.5)	45 (10.2)	26 (5.9)	81 (18.4)	
Age (y)*	52.2 ± 11.2	53.3 ± 10.3	49.2 ± 12.4	50.4 ± 8.3	52.7 ± 11.3	.073
Tumor size (mm)*	22.4 ± 14.6	20.1 ± 12.8	24.5 ± 12.9	34.4 ± 26.7	25.5 ± 13.9	<.001
No. of tumors by grade						<.001
Low	91 (21.0)	82 (29.6)	3 (6.7)	1 (4.0)	2 (2.6)	…
Intermediate	218 (50.2)	155 (54.0)	25 (55.6)	13 (52.0)	25 (32.5)	…
High	125 (28.8)	47 (16.3)	17 (37.8)	11 (44.0)	50 (64.9)	…

Note.—Data in parentheses are percentages. There were five patients with missing tumor sizes and seven patients with missing tumor grades.

* Data are mean ± standard deviation.

Table 3

Distribution of Pathologic Analysis–proven MR Imaging Findings according to Surrogate Molecular Subtype

Parameter	All Subtypes	Surrogate Molecular Subtype				*P* Value
		Luminal A	Luminal B	HER2	Basal	
No. of patients	441	289 (65.5)	45 (10.2)	26 (5.9)	81 (18.4)	
No. of multifocal or multicentric diseases	142 (32.2)	79 (27.3)	24 (53.3)	17 (65.4)	22 (27.2)	<.001
No. of tumors with lymph node involvement	95 (21.5)	50 (17.3)	16 (35.6)	9 (34.6)	20 (24.7)	.014
No. of tumors with skin or nipple invasion	15 (3.4)	11 (3.8)	3 (6.7)	0 (0)	1 (1.2)	.203
No. of tumors with chest wall or pectoralis muscle invasion	6 (1.3)	3 (1.0)	2 (4.4)	0 (0)	1 (1.2)	.396
No. of tumors with contralateral disease	17 (3.9)	14 (4.8)	1 (2.2)	1 (3.8)	1 (1.2)	.375

Note.—Data in parentheses are percentages.

from specific breast cancer molecular subtype of each patient. Our study provides an additional step in this direction by identifying clinically important findings among different molecular subtypes that may help direct the use of breast MR imaging in the preoperative setting.

Identification of multifocal and multicentric disease in the breast is important because these findings may represent contraindications to breast conservation therapy (19), and total tumor burden is an independent predictor of local recurrence, metastatic disease, and overall survival (30,31). However, the use of MR imaging to help to detect ipsilateral disease beyond the primary tumor (32) has thus far not produced corresponding benefits in patient outcomes (2,7,33). Our data provide a potential explanation for this discrepancy by determining that multifocal and multicentric disease is more commonly found in luminal B and HER2 subtypes, even after controlling for patient age, tumor size, and tumor grade. Previous work that studied MR imaging outcomes (2,7,33) included limited receptor data and did not analyze cancers by molecular subtypes. Luminal A subtype represents the majority of breast cancers, yet has the lowest pretest probability of multifocal and/or multicentric disease, the greatest sensitivity to endocrine and radiation therapies (13,15), and the best prognosis (14). When all molecular subtypes are pooled for analysis, the influence of the luminal A subtype may obscure the potential benefits of preoperative MR imaging. A clinical benefit may be more evident if preoperative MR imaging is used in patients with luminal B and HER2 subtype breast cancers because these patients are more likely to have clinically significant disease, where changes in treatment strategies may affect clinical outcomes. Future prospective studies that evaluate the benefits of preoperative MR imaging should incorporate molecular subtype data into analysis of clinical outcomes to better understand its value.

While breast cancer subtypes have become essential to guide systemic therapy, nodal status (presence or absence of metastatic disease to axillary nodes) remains important to decide the sequence (preoperative sequence vs postoperative sequence), type (endocrine, chemotherapy, and/or targeted therapy), and extent (agents and number of cycles) of systemic therapy (19,34). Nodal status also assists in estimation of prognosis and the consequent benefits of systemic therapies. Clinical approaches to evaluation and management of the axilla in early stage breast cancer are evolving and are

Table 4

Multivariate Logistic Regression Analysis

	Multifocal or Multicentric Disease		Lymph Node Involvement	
Parameter	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Molecular subtype		<.001		.224
Luminal A	1.0	…	1.0	…
Luminal B	2.8 (1.4, 5.4)	…	1.7 (0.8, 3.6)	…
HER2	4.1 (1.7, 10.4)	…	1.9 (0.7, 5.0)	…
Basal	0.8 (0.4, 1.5)	…	0.8 (0.4, 1.6)	…
Tumor grade		.828		.020
Low and/or intermediate	1.0	…	1.0	…
High	1.1 (0.6, 1.8)	…	1.9 (1.1, 3.4)	…
Tumor size	0.99 (0.98, 1.00)	.051	1.04 (1.02, 1.06)	<.001
Age	1.00 (1.00, 1.00)	.384	1.00 (1.00, 1.00)	.029

Note.—Data in parentheses are 95% confidence intervals. There were five patients with missing tumor sizes and seven patients with missing tumor grades that were excluded from the multivariate analysis.

guided by studies that support less aggressive surgical management (35) and more aggressive radiation therapy in node-positive disease (36). Our study found that preoperative breast MR imaging helped to show significantly more frequent, pathologic analysis–confirmed metastatic lymph node involvement in luminal B and HER2 subtype (ie, HER2 positive) breast cancer. Because the diagnostic yield is greater in HER2 and luminal B subtypes, the clinical use of MR imaging to help guide treatment planning (eg, axilla management and systemic therapy) may be greater for the HER2 and luminal B subtypes and could affect clinical outcomes.

Formal genomic analysis is the standard for the classification of molecular subtypes and is shown to be more robustly predictive of breast cancer outcomes (17). However, this analysis relies on evaluation of the expression of thousands of genes, which is time consuming, expensive, and may not be universally available. The molecular assays currently available for clinical use rely on a small number of genes but have limited clinical use. For example, the most commonly used prognostic molecular assay (Oncotype Dx; Genomic Health, Redwood City, Calif) analyzes 21 genes, but is used only for ER-positive tumors. However, ER, PR, and HER2 expression are measured routinely in all new breast cancer cases and are closely associated with formal molecular subtype profiles (17,18). This makes surrogate classification of molecular subtypes readily available and easily applied toward clinical decision making. Our data showed differences in extent of disease among molecular subtypes by using preoperative MR imaging, which has potential implications for managing local-regional and systemic therapy on the basis of this surrogate marker analysis.

There are several limitations to our study. Our study design did not collect patient outcome data, which would be an important next step to evaluate the relationship between breast cancer molecular subtype and preoperative MR imaging. In addition, because this was a retrospective, single-institution study, we could not control for possible selection bias for patients undergoing preoperative breast MR imaging; however, the distribution of molecular subtypes in our sample was similar to that reported by multiple previous investigators (16,17,24). Further, interpreting radiologists had access to the full medical record at the time of original interpretations (2006–2009), which may have provided them with knowledge of molecular subtype during interpretation. However, because of limited emphasis of any relationship between breast cancer molecular subtype and MR imaging at that time, it is unlikely that interpretations were influenced. Our study was also limited to the use of pathologic data that was routinely reported between 2006 and 2009, and therefore newer, potentially predictive variables, such as Ki-67, were not included for analysis. Finally, although we had a large sample size (n = 441), the number of patients with contralateral disease (n = 17), chest wall or pectoralis muscle invasion (n = 7), and skin or nipple invasion (n = 15) was much smaller. It is possible that differences between subtypes of these variables may be identified in a larger set of data.

In conclusion, preoperative breast MR imaging is significantly more likely to help to detect multicentric or multifocal disease and lymph node involvement in luminal B and HER2 molecular subtype breast cancers on the basis of surrogate biomarkers. Further studies to prospectively evaluate the role of molecular subtype in preoperative breast MR imaging and to assess the effect on patient outcomes are warranted. Molecular subtype may be an important consideration for clinicians when preoperative MR imaging for a new diagnosis of breast cancer is considered because MR imaging is more likely to depict additional sites of disease, which could change treatment in patients with specific cancer profiles.

Disclosures of Conflicts of Interest: L.J.G. disclosed no relevant relationships. **K.S.J.** disclosed no relevant relationships. **P.K.M.** disclosed no relevant relationships. **J.A.B.** disclosed no relevant relationships. **M.S.S.** disclosed no relevant relationships.

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