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MINIREVIEWS

How to use magnetic resonance imaging following neoadjuvant chemotherapy in locally advanced breast cancer

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Abstract

Magnetic resonance imaging (MRI) is highly sensitive in identifying residual breast cancer following neoadjuvant chemotherapy (NAC), and consequently is a commonly used imaging modality in locally advanced breast cancer patients. In these patients, tumor response is an important prognostic indicator. However, discrepancies between MRI findings and surgical pathology are well documented. Overestimation of residual disease by MRI may result in greater surgery than is actually required while underestimation may result in insufficient surgery. Thus, it is important to understand when MRI findings are reliable and when they are less accurate. MRI most accurately predicts pathology in triple negative, Her2 positive and hormone receptor negative tumors, especially if they are of a solid imaging phenotype. In these cases, post-NAC MRI is highly reliable for surgical planning. Hormone receptor positive cancers and those demonstrating non mass enhancement show lower concordance with surgical pathology, making surgical guidance more nebulous in these cases. Radiologists and surgeons must assess MRI response to NAC in the context of tumor subtype. Indiscriminate interpretations will prevent MRI from achieving its maximum potential in the pre-operative setting.

Key words: Breast; Magnetic resonance imaging; Neoadjuvant chemotherapy; Biomarkers; Phenotypes

Core tip: Following neoadjuvant chemotherapy, breast magnetic resonance imaging (MRI) most accurately predicts surgical pathology in triple negative, Her2 positive and hormone receptor negative tumors, especially if they are of a solid imaging phenotype. In these cases, post-neoadjuvant chemotherapy (NAC) MRI is highly reliable for surgical planning. Hormone receptor positive cancers and those demonstrating non mass enhancement show lower concordance with surgical pathology, making surgical guidance more nebulous in

these cases. Radiologists and surgeons must assess MRI response to NAC in the context of tumor subtype.

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INTRODUCTION

Breast cancer is a heterogeneous disease consisting of many different tumor subtypes, each with its own biology, prognosis, and treatment options. These subtypes are characterized by distinct molecular profiles, proliferation rates, and tumor receptors, including estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). In today's paradigm of personalized medicine, biomarker profiles allow tailoring treatment strategies to the individual tumor. Current treatment of locally advanced breast cancers includes chemotherapy, hormone therapy [if hormone receptor (HR) positive] and surgical resection. Increasingly, chemotherapy is given prior to surgery. Neoadjuvant chemotherapy (NAC) offers advantages in terms of adding prognostic information and improving surgical options. Tumor response to NAC is an important prognostic indicator. Patients who have a pathologic complete response (pCR) following NAC have improved overall survival, disease-free survival and recurrence-free survival[1-6]. NAC can also facilitate breast-conserving surgery in patients whose initial presentation may have warranted mastectomy[7-9]. Even if patients still have residual disease, especially if they need radiation, breast conservation will have fewer complications than mastectomy and radiation. As treatments improve and responses to NAC become more common, a new challenge arises - accurately determining the extent of surgical resection needed to excise residual tumor. Magnetic resonance imaging (MRI) is highly sensitive in identifying residual disease following NAC, with multiple studies demonstrating it to be more accurate than mammography, ultrasound or physical examination[10-16]. Consequently, MRI is a commonly used imaging modality in locally advanced breast cancer patients.

In these patients, pre-operative MRI is an important addition to the decision-making armamentarium. The appearance of breast cancer on MRI can be classified by its morphology into phenotypic categories[17], which are associated with response to NAC and ability to offer breast-conserving surgery[17,18]. Overall, MRI has been shown to be the most sensitive imaging modality by which to follow a patient's response to NAC and to be more sensitive than clinical examination[11-16,19-23]. While an excellent test, MRI is far from perfect. Discrepancies between MRI findings and surgical pathology are well documented. Overestimation of residual disease by MRI may result in greater surgery than is actually required (larger lumpectomies, wider margins, mastectomy)[1,24]. Underestimation may result in insufficient surgery, resulting in positive margins and re-excisions[1]. Thus, it is important to understand when MRI findings [particularly radiologic complete responses (rCR)] are reliable and when they are less accurate.

The general question of the accuracy of an rCR to predict a pCR may be overly broad - accuracy needs to be considered in the context of tumor subtype. Literature has shown that the accuracy of post-NAC MRI is related to tumor subtype, with the strongest evidence arising from multi-institutional trials like I-SPY[18] and Translational Breast Cancer Research Consortium Trial 017[25], as well as additional support from multiple single-institution studies[26-29]. A smaller literature base suggests that MRI phenotype is also related to the accuracy of MRI in the post-NAC, pre-operative setting.

In this manuscript, we review the evidence for accuracy of post-NAC MRI findings and focus on how best to use MRI in this setting, specifically for the evaluation of extent of disease and pCR. In particular, this review will evaluate the association between the diagnostic performance of MRI in the post-NAC setting and the biomarker profile of the tumor, as well as the association between pre-NAC phenotypic tumor appearance on MRI and diagnostic accuracy. A clear understanding of these relationships can be valuable in setting appropriate treatment goals and expectations[18]. In much the same way each breast cancer requires a tailored treatment strategy, a strategy for tailored imaging interpretation should also be employed and would enable more accurate recommendations to be made for individual patients.

ASSOCIATIONS WITH MRI PHENOTYPE

The relationship between phenotypic MRI appearance of breast cancers and response to NAC has been studied[17,29]. Although phenotypic categorizations vary slightly, in general, phenotypes tend to focus on the separation of solid and well-contained unifocal (Figure 1A) and multifocal masses from more diffuse and infiltrative non-mass enhancement (NME) (Figure 1B)[17,18,29]. These phenotypes impact NAC response, with well-defined mass phenotypes more likely to have a response sufficient to allow for breast conserving surgery[17,18]. Well-defined masses also show higher concordance between MRI and surgical pathology, with an rCR in the setting of solid phenotypes (particularly hormone-negative tumors) predictive of a corresponding pCR at surgery[18]. On the other hand, MRI is less accurate in predicting pCR in tumors presenting as non-mass/diffuse enhancement, with larger discrepancies between post-NAC MRI and surgical pathology[18].

Studies have also suggested that these differing phenotypic appearances have particular patterns of

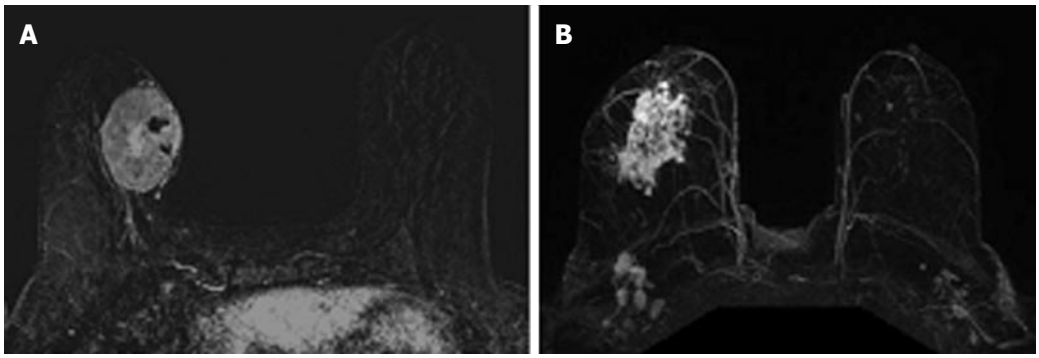

Figure 1 Magnetic resonance imaging phenotypes solid unifocal mass (A) and more diffuse non-mass enhancement (B).

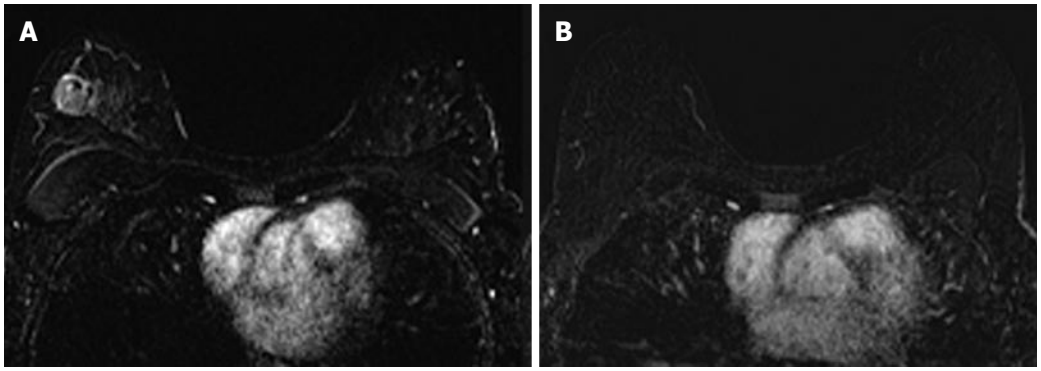

Figure 2 Forty-two years old woman with triple negative right breast cancer. A: Baseline axial T1-weighted post-gadolinium fat-saturated magnetic resonance image demonstrates a 3.6 cm unifocal mass in the upper outer quadrant; B: Post-neoadjuvant chemotherapy magnetic resonance imaging demonstrates complete resolution of the mass seen previously. Surgical pathology demonstrates biopsy site changes and expected changes related to chemotherapy with no evidence of residual cancer.

response to NAC[17,24,29-31]. Locally advanced malignancies presenting as a mass lesion often shrink in a concentric pattern to a smaller mass. Following NAC, NME often diminishes to a scattered pattern of residual disease that can extend throughout the original area of involvement, though as small foci that are difficult to detect on MRI. Residual infiltrating single cells will likely not be visible on MRI.

The associations between MRI accuracy and phenotype are likely confounded by tumor biomarker status. Comparisons of MRI phenotypes relative to tumor biomarker profiles[18,24,28,29,32,33] have shown a number of trends, with an association between unifocal mass presentation and triple negative tumors (TN: ER negative, PR negative, Her2 negative) (Figure 2). Multifocal mass presentation is more common in HER2+ (and questionably in HR positive) tumors. Although they do not have a characteristic phenotypic presentation, HR positive cases, especially ER positive tumors, are more likely to present as non mass/diffuse enhancement compared to other subtypes (Figures 3 and 4). Although these relationships have been demonstrated, all phenotypes are seen in all biomarker profiles[18].

ASSOCIATIONS WITH TUMOR BIOMARKERS

Extent of disease evaluation

The impact of tumor biomarkers on the accuracy of MRI for detecting the extent of disease must be considered when interpreting post-NAC MRI in anticipation of surgical resection. In addition to the individual status of receptors, biomarkers can categorize tumors into different subtypes. Tumor subtypes include luminal (ER/PR positive, Her2 negative), Her2 positive, and basal (ER/PR/Her2 negative; analogous to TN.) Multiple studies have demonstrated that in the post-NAC setting, the MRI assessment of extent of residual disease is most accurate in tumors that are either TN (Figure 2) or Her2 positive.

McGuire *et al*[26] retrospectively reported their institutional experience and found that MRI was most accurate in estimating pathologic size of residual disease in the Her2 positive and TN subtypes. Additionally, they found that MRI was more likely to underestimate the amount of residual disease in the luminal subtype (ER/PR positive, Her2 negative) when compared with TN or Her2 positive tumors. In a study done by Loo *et al*[29], MRI findings correlated well with the pathologic findings in the TN and Her2 positive breast cancers, but not with ER positive or Her2 negative breast cancers. Kuzucan *et al*[24] evaluated only Her2 negative cancers, and report similar findings-higher concordance between post-NAC tumor size on MRI and pathologic size in HR negative tumors compared to HR positive tumors. In Kuzucan's study, MRI accuracy was also increased in tumors expressing high levels of the proliferation marker Ki-67 (defined as > 40% positive). A study by

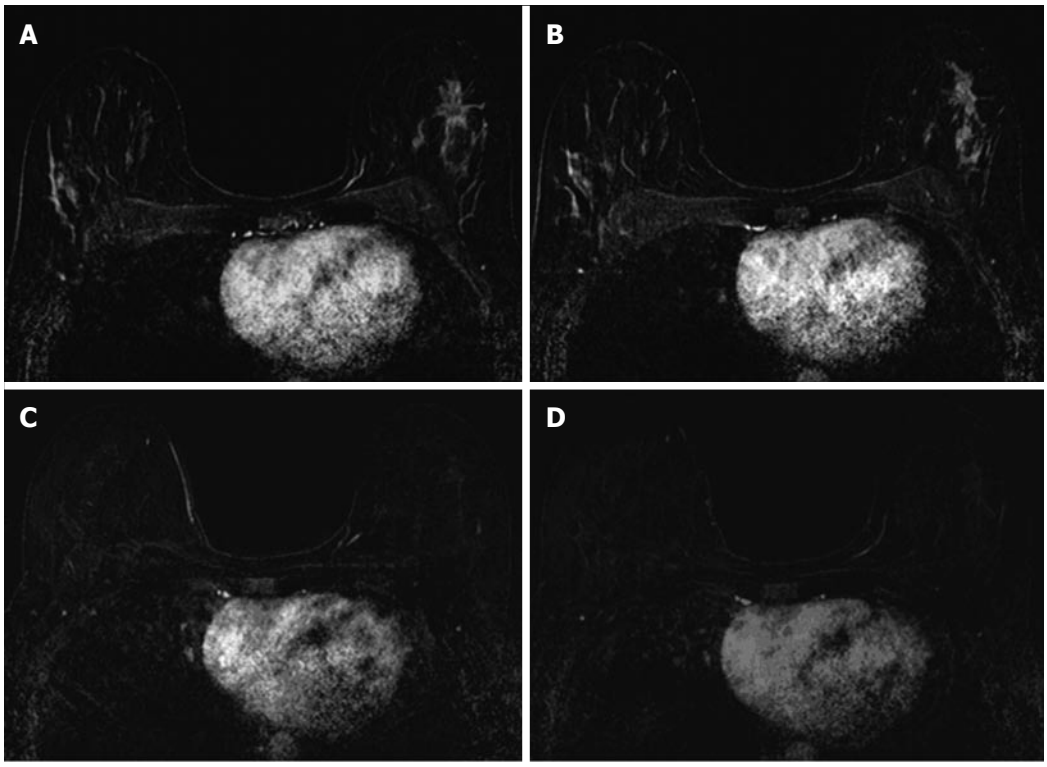

Figure 3 Thirty-seven years old woman with HR+ left breast cancer. A and B: Baseline axial T1-weighted post-gadolinium fat-saturated magnetic resonance image demonstrates a speculated mass and contiguous non-mass enhancement extending posteriorly for a total of 7 cm of disease in the upper outer breast; C and D: Post-neoadjuvant chemotherapy magnetic resonance imaging demonstrates decrease in size and degree of enhancement of prior findings. Surgical pathology demonstrates 6.9 cm of invasive ductal carcinoma.

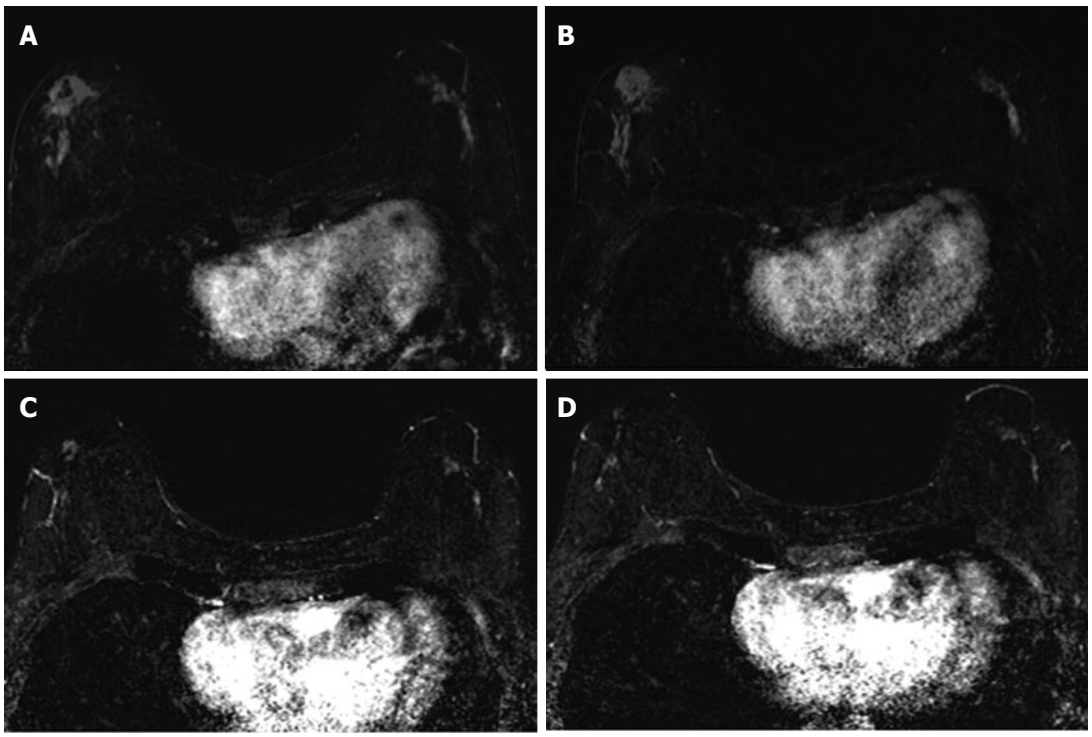

Figure 4 Sixty-four years old woman with bilateral HR+ breast cancer. A and B: Baseline axial T1-weighted post-gadolinium fat-saturated magnetic resonance image demonstrates 3.2 cm irregular mass and contiguous non-mass enhancement (NME), spanning up to 7.2 cm, in the right central outer breast and 3.5 cm of clumped linear NME in the central outer left breast; C and D: Post-neoadjuvant chemotherapy magnetic resonance imaging demonstrates decrease in size of the right breast mass and NME. NME in the left breast demonstrates only mild improvement. Surgical pathology demonstrates 4.3 cm of residual disease on the right and 3.7 cm of disease on the left.

Kim *et al*[34], which investigated TN cancer, also found that Ki-67 affects the diagnostic accuracy of MRI, with higher correlation between MRI and residual tumor size at surgery in Ki-67 positive patients.

In I-SPY, a multicenter neoadjuvant trial with serial MRIs over the course of therapy, there were the fewest discrepancies between the post-NAC MRI tumor size and pathologic size in Her2 positive, HR negative, and TN tumors[18]. Overall, 38% of patients analyzed had a size discrepancy of at least 2 cm between MRI and surgical pathology, with two thirds of these discrepancies being an overestimation of disease on MRI. These size discrepancies were significantly more common in HR+/Her2- tumor subtypes. Additionally, size discrepancies differed by MRI phenotype; among the solid phenotypes, underestimation of disease by 1.5 cm or more was rare. These Her2+, HR-, and TN tumors were also the tumor subtypes most likely to have a substantial response to NAC. The experience at our institution is in accordance with other published reports. In cases of Her2 positive, HR negative, and TN tumors, if there is residual disease on MRI, it is highly likely that there will be residual disease in the surgical specimen. Underestimation of disease in these subtypes is rare, particularly in the triple negative group where no false negative MRI's were seen.

pCR evaluation

Apart from measuring residual disease for the purposes of surgical planning, the ability of MRI to predict a pathologic complete response (pCR), a surrogate for improved outcome, is of particular importance in breast cancer management. Attaining pCR gives prognostic information that can be used for decision making, including the type of surgical procedure and/or reconstruction to recommend, and is also used as an immediate endpoint in evaluating the efficacy of NAC. Data show that pCR is associated with improved outcomes, and is more predictive when assessed by individual tumor subtype than for all subtypes combined[1,35]. A non-invasive method to accurately determine whether or not a pCR had been achieved would potentially change how trials are designed, and could eventually change surgical management of breast cancer.

While MRI accuracy depends on both its positive predictive value (PPV), and its negative predictive value (NPV), the NPV becomes the most important variable if the goal is to spare a patient invasive treatment in the setting of an rCR. That is, one must be able to trust that a negative MRI is a true negative in order to safely omit surgical resection or other treatment. In the reported papers looking at the accuracy of MRI for predicting pCR in the post-NAC setting, one must note that relatively high accuracy is possible with a low NPV. This can occur when MRI has a very high PPV, ultimately leading to high accuracy despite low NPV. In tumor subtypes that are less likely to respond to NAC, such as luminal tumors, the likelihood of residual disease is high, resulting in high PPV. However, the chance of a false negative is also highest in this group, so despite high apparent accuracy (driven by PPV), an rCR should be interpreted with caution (Figures 3 and 4).

Just as the accuracy of MRI in predicting extent of disease differs by tumor subtype, it appears that the ability of MRI to accurately predict pCR also differs by tumor subtype[24]. The NPV of MRI for predicting pCR differs by tumor subtype, highest in HR negative/Her2 positive tumors and triple negative (Figure 2) tumors[18,24-26,36]. In our report of I-SPY patients, when the post-NAC MRI underestimated residual disease (which occurred 4.3% of the time), all the discordant cases were either HR positive (Figures 3 and 4) or had diffuse phenotypes (Figure 4)[18].

Recently, several groups have reported on the accuracy of post-NAC MRI for correctly identifying pCR. Of note, some groups define pCR as the absence of any invasive tumor cells (the preferred definition of the FDA)[37], while others require the absence of both invasive and *in situ* disease - this definition must be noted when interpreting study findings, as residual *in situ* disease may lead to higher local recurrence rates[38].

One retrospective multicenter study of 746 women undergoing NAC found overall NPV for MRI of 47% and accuracy of 74% for predicting pCR[25]. The NPV for MRI varied by tumor subtype, and was highest amongst HR-/Her2+ tumors (62%) and TN tumors (60%). The overall accuracy was highest for HR+/Her2 negative tumors, likely because the PPV in this group was 91%. This likely reflects the fact that because this subtype is the least likely to respond to NAC, the pretest probability for having residual disease is higher.

Single institution studies have shown similar results. Chen *et al*[27] demonstrated the vast difference in MRI accuracy by tumor subtype, with accurate prediction of pCR in 95% of Her2 positive tumors, but only in 50% of Her2 negative tumors. Kim *et al*[34] found MRI accurately predicted pCR in 91% of TN cases. Kuzucan *et al*[24] focused on Her2 negative patients, and also found higher accuracy in HR negative tumors, with a PPV of 88% and NPV of 88%. In HR positive tumors, MRI had a PPV of 100% but an NPV of only 56%. The authors noted that the higher NPV in the HR negative tumors may have been related to a higher prevalence of solid tumor phenotypes, acknowledging that tumor phenotype impacts MRI accuracy and response to NAC[24]. In Ko *et al*[28]'s 2013 report, overall PPV was 89.6% and NPV was 83.8%. Of the five false negative MRI's in their study, 3 were ER positive, 2 were Her2 positive, and 3 initially appeared as non mass enhancement. The most recent report, by Bufi *et al*[36] in 2014, shows the highest NPV rates to date. In the TN tumor subtypes, they report NPV of 100%. In the Her2 positive subtype, they report NPV of 100% using diffusion weighted imaging, suggesting that newer advanced MRI techniques may improve accuracy of MRI in different subtypes[36].

CONCLUSION

MRI most accurately predicts pathology in TN, Her2 positive and HR negative tumors, especially if they are of a solid imaging phenotype. In these cases, post-NAC MRI is highly reliable for surgical planning. Hormone receptor positive cancers and those demonstrating NME demonstrate lower concordance with surgical pathology, making surgical guidance more nebulous in these cases.

While MRI may not yet meet the necessary NPV threshold to safely allow for omission of surgical treatment, this may be feasible for specific tumor subtypes in the future. It is unclear whether or not the differential accuracy of MRI by tumor subtype is mediated by tumor phenotype, tumor response to NAC, or biological differences that affect imaging, or possibly by all of these factors. Regardless, it is clear at this point that radiologists and surgeons must assess MRI response to NAC in the context of tumor subtype. If imaging interpretations are not made in this context, pre-operative MRI will continue to be limited by both overestimation and underestimation of residual disease. The same way each breast cancer requires a tailored treatment strategy, tailored interpretation strategies should also be employed. Future work on redefining thresholds for enhancement interpretation based on tumor biology and on the development of receptor subtype-based imaging protocols may improve accuracy in the future.

With the understanding that pCR predicts recurrence free survival, if an rCR can confidently predict pCR (as in TN and Her2 positive tumors), then an rCR can predict recurrence free survival. As an imaging predictor for such important outcomes, MRI interpreted in the context of tumor subtype would be a tremendous asset in decision-making and patient counseling.

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