original reports abstract

Clinical Utility of a Hand-Held Scanner for Breast Cancer Early Detection and Patient Triage

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PURPOSE Globally, breast cancer represents the most common cause of cancer death among women. Early cancer diagnosis is difficult in low- and middle-income countries, most of which are unable to support population-based mammographic screening. Triage on the basis of clinical breast examination (CBE) alone can be difficult to implement. In contrast, piezo-electric palpation (intelligent Breast Exam [iBE]) may improve triage because it is portable, low cost, has a short learning curve, and provides electronic documentation for additional diagnostic workup. We compared iBE and CBE performance in a screening patient cohort from a Western mammography center.

METHODS Women presenting for screening or diagnostic workup were enrolled and underwent iBE then CBE, followed by mammography. Mammography was classified as negative (BI-RADS 1 or 2) or positive (BI-RADS 3, 4, or 5). Measures of accuracy and κ score were calculated.

RESULTS Between April 2015 and May 2017, 516 women were enrolled. Of these patients, 486 completed iBE, CBE, and mammography. There were 101 positive iBE results, 66 positive CBE results, and 35 positive mammograms. iBE and CBE demonstrated moderate agreement on categorization ($\kappa = 0.53$), but minimal agreement with mammography ($\kappa = 0.08$). iBE had a specificity of 80.3% and a negative predictive value of 94%. In this cohort, only five of 486 patients had a malignancy; iBE and CBE identified three of these five. The two cancers missed by both modalities were small—a 3-mm retro-areolar and a 1-cm axillary tail.

CONCLUSION iBE performs comparably to CBE as a triage tool. Only minimal cancers detected through mammographic screening were missed on iBE. Ultimately, our data suggest that iBE and CBE can synergize as triage tools to significantly reduce the numbers of patients who need additional diagnostic imaging in resource-limited areas.

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INTRODUCTION

Globally, breast cancer remains the most prevalent and leading cause of cancer death in women.[1] Survival varies significantly as a result of the stage at diagnosis and access to treatment in different geographic regions.[2-4] In high-income countries, mammography is used for population-based screening. Unfortunately, mammography is expensive and resource intensive, requiring extensive infrastructure to link screening with additional diagnostic workup. In addition, breast cancer in low- and middle-income countries (LMICs) commonly presents in women younger than age 45 years for whom mammography is not recommended for screening because of decreased sensitivity. Early detection strategies not dependent on mammographic screening are urgently required.

In LMICs, patient triage methods are used to identify women who would benefit from diagnostic imaging and workup. In much of Asia, Africa, and Latin America,[5-7] cancers are typically discovered by the woman herself or found on clinical breast exam (CBE) by community health workers and often are late stage at the time of diagnosis. Referral from the primary care facility to a higher-level center where diagnostic workups can be performed is often problematic, poorly standardized, and promotes significant delays.[8-10] In most LMICs, community health workers and primary care providers lack the knowledge and skills regarding breast cancer diagnosis[11] and report limited confidence in their abilities to perform CBE.[10] Implementation studies of CBE in LMICs have shown efficacy in screening and detection but failure in the diagnostic follow-up phase.[12,13] A method with which to standardize these exams and associate patients with an exam report would make the linkage to additional diagnostic testing more reliable.

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CONTEXT

Key Objective

How does the intelligent Breast Exam (iBE; a low-cost, portable, palpation-based breast cancer detection device) perform compared with standard clinical breast exam (CBE) and mammography in a Western screening population?

Knowledge Generated

iBE and CBE had similar performance characteristics, but both had more false positive results than did the gold standard of mammography. Triage for additional imaging—with ultrasound or mammogram—on the basis of iBE and CBE would have detected three of the 5 cancers in this screening cohort while reducing the overall imaging pool by 80%.

Relevance

With its mobile digital platform and reproducibility, iBE has the potential to synergize with CBE and point-of-care ultrasound for triage in screening programs in low- and middle-income countries. Implementation studies in low- and middle-income countries are the next step in evaluation.

The iBreast Exam device (intelligent Breast Exam [iBE]) was introduced and received US Food and Drug Administration approval in 2013 as a tool for documenting clinical findings in the breast. Outside the United States, iBreast was developed as an inexpensive and portable breast exam tool to be used by health care workers with minimal training. Its piezoelectric finger technology measures differences in breast tissue stiffness using tactile palpation from the skin surface. Results are stored instantly on a tablet or smartphone and uploaded to the cloud whenever possible. In a proof-of concept study, a prototype iBE probe was able to detect clinically significant breast lesions with a sensitivity of 87%.[14] In a second validation study, a production iBE probe demonstrated a sensitivity of 85.7% for clinically significant lesions in 78 patients.[15] The current study was designed to demonstrate the performance of iBE as a triage device in the LMIC setting by testing in a large asymptomatic population of women presenting for routine, state-of-the-art screening in the United States.

METHODS

Study Design

This study was designed to assess whether iBE can be used to reduce the pool of women who need follow-up and diagnostic services by correctly screening out women with normal mammograms without missing patients with clinically significant invasive cancers. We hypothesized that iBE would adequately identify these normal or true negatives in this population, reported here as specificity. Those patients with abnormal findings on mammography—not limited to cancers—were classified as positive in this study. Adequate identification of positive patients in this population was reported here as sensitivity. As this was an asymptomatic screening population in a Western center, the study was not powered to determine cancer detection precision; however, our results for the few malignancies identified are reported below.

This single-site prospective nonrandomized study was approved by the University of Pennsylvania Institutional Review Board (protocol #821412) and the Abramson Cancer Center Clinical Trials Scientific Review Committee (University of Pennsylvania Cancer Center #24114). All patients signed informed consent forms before participation. Patients presenting to the University of Pennsylvania's imaging center for a screening, diagnostic, and interventional procedure were eligible to participate. Patients younger than age 18 years were excluded. Enrolled patients were brought to an exam room where first a bilateral iBE exam and then a bilateral CBE were performed by the same trained technologist who was blinded to all radiologic exam results. Patients were examined in supine position. Results from iBE exams had no impact on clinical decisions.

Multimodal breast screening at the University of Pennsylvania includes screening mammography, diagnostic mammography, high-quality ultrasound diagnostics, breast magnetic resonance imaging, and/or biopsy when indicated. For asymptomatic women with a negative screening mammogram, regular-interval follow-up is recommended. For patients with an abnormal screening mammogram or palpable masses, a diagnostic mammogram was performed in women older than age 40 years; diagnostic ultrasound was used in women with palpable masses. In women younger than age 35 with a palpable mass, ultrasound was performed in place of mammography.

iBE Device

The iBE is a battery-powered, electrically insulated device, with a maximum voltage of 5 V and maximum current of 1 mA. It consists of a hand-held compression probe containing a 4×4 array of piezoelectric fingers, a custom-built electronics board, and a tablet. The iBE communicates wirelessly with the tablet to display findings in real time, store and share data digitally, and compare findings with past results. The piezoelectric finger technology consists of tactile pressure sensors that measure tissue compression by electrical displacement when tactile palpations are made in a top-down fashion against the breast surface.

iBE results are displayed in a 4 × 4 pressure array map of the breast on the tablet. Areas of green indicate normal tissue while any area of red indicates a detected lesion. The iBE does not characterize the type of lesion detected. In real-world applications, patients with red pressure arrays would be triaged for additional testing. iBE evaluations were conducted by a technologist who was trained by the manufacturer who reviewed the functions of the device and guided practice on breast phantoms, followed by 10 observed iBE studies with the principal investigator.

Data Collection and Classification

Results from the iBE and CBE were recorded in case report forms at the time of the exams. Results from mammography exams were accessed through the electronic medical record. Patient age, body mass index, bra size, surgical history, and results of all imaging studies were entered into a study database. CBE, iBE, and mammogram exam results were classified as either negative or positive for comparative statistical analyses. A green pressure array map on iBE was classified as negative, whereas any area of red pressure array on the iBE map was classified as a positive exam. Absence of a palpable lesion on CBE was classified as negative, whereas the presence of any clinically palpable lesion on CBE was classified as a positive exam. No findings or benign findings on mammography (BI-RADS 1 and 2) were classified as negative, and suspicious microcalcifications, asymmetries, or masses on mammography (BI-RADS 3,4, or 5) were classified as a positive exam.

Statistical Analysis

Measures of diagnostic accuracy, including sensitivity, specificity, negative predictive value, and positive predictive value, were calculated. CIs are reported where appropriate. κ scores were calculated and reported as a measure of agreement between the categories assigned by each test.

RESULTS

From May 2015 through April 2017, 516 patients consented to participate in the study. Thirty patients were excluded for failure to complete all 3 screening exams (iBE, CBE, and mammography). Mean age of the 486 included patients was 58 years (range, 30 to 89 years). The racial and ethnic distributions of patients are listed in Table 1. Overall, there were 101 positive iBE results, 66 positive CBE results, and 35 positive mammogram results (BI-RADS 3,4, or 5); 45 patients also underwent ultrasound, 7 underwent magnetic resonance imaging, and 22 underwent biopsy for additional diagnostic workup.

For the iBE and CBE comparison (Table 2; $\kappa = 0.54 \pm 0.04$), 370 patients had a negative result on both iBE and CBE, and 51 patients had a positive result on both iBE and CBE. For the iBE and mammogram comparison (Table 3; $\kappa = 0.08 \pm 0.04$), 362 patients had a negative result on both iBE and mammogram, producing a specificity for predicting a negative mammogram of 80.3% (range, 76.5% to 83.9%), corresponding to a false positive rate of 19.7% and a negative predictive value of 94.0%. Twelve patients had a positive result on both iBE and mammogram, producing a sensitivity for predicting a positive mammogram (BI-RAD 3, 4, or 5) of 34.3% (range, 18.6% to 50.0%).

For the CBE and mammogram comparison (Table 4; $\kappa = 0.16 \pm 0.04$), 397 patients had a negative result on both CBE and mammogram, producing a specificity for predicting a negative mammogram of 88.0% (range, 85.0% to 91.0%). This corresponds to a false positive rate of 12.0% and a negative predictive value of 94.5%. There were 12 patients with a positive result on both CBE and

TABLE 1. Characteristics of Study Participants

Characteristic	N = 486
Mean age, years (range)	58 (30-89)
Race	
White	312 (64.2)
African American	153 (31.5)
Asian	9 (1.9)
American Indian	2 (0.4)
Pacific Islander	1 (0.2)
Mixed race	2 (0.4)
Unknown	7 (1.4)
Ethnicity	
Hispanic	17 (3.5)
Non-Hispanic	468 (96.3)
Unknown	1 (0.2)
Body mass index	
< 18.5	9 (1.9)
18.5 to < 25.0	165 (33.9)
25.0 to < 30.0	137 (28.2)
≥ 30.0	175 (36.0)
Positive exam	
iBE	101 (20.8)
CBE	66 (13.6)
Mammogram	35 (7.2)

NOTE. Data are presented as No. (%) unless otherwise noted.
Abbreviations: CBE, clinical breast examination; iBE, intelligent Breast Exam.

TABLE 2. iBE Versus CBE for Positive Exam Detection

Value	CBE (+)	CBE (–)	Measure
iBE (+)	51	50	
iBE (–)	15	370	
Measure			$\kappa = 0.53$

Abbreviations: CBE, clinical breast examination; iBE, intelligent Breast Exam.

TABLE 3. iBE Versus Mammogram for Positive Exam Detection

Value	Mammogram (+)	Mammogram (–)	Measure
iBE (+)	12	89	
iBE (–)	23	362	NPV = 94.0%
Measure		Sp = 80.3%	κ = 0.08

Abbreviations: iBE, intelligent Breast Exam; NPV, negative predictive value; Sp, specificity.

mammogram, producing a sensitivity for predicting a positive mammogram (BI-RAD 3,4, or 5) of 34.3% (range, 18.6% to 50.0%)

After completion of all three screening exams and additional diagnostic workup for those patients who required it, all 486 patients were assigned a final diagnosis as shown in Table 5. Although right and left breasts were individually examined, these diagnoses represent a whole patient analysis. Of patients, 449 received a final diagnosis of no findings or benign findings. Twenty patients had a cyst, and fibroadenoma was found in 7 patients. Benign microcalcifications were found in 2 patients, and atypical hyperplasia was diagnosed in 1 patient. An initial diagnosis of undefined mass was assigned to 2 patients. The first undefined mass was not biopsied but instead recommended for short-term follow-up imaging, and the second mass was granulomatosis with polyangiitis. Finally, ductal in situ carcinoma (DCIS) or breast cancer was diagnosed in 5 patients.

In the 5 patients with a final diagnosis of DCIS or breast cancer, 7 separate malignancies were diagnosed because 2 of these 5 patients presented with bilateral breast cancers (Table 6). Four of the 7 malignant lesions were detected by both iBE and CBE. Three of the 7 malignant lesions went undetected by both iBE and CBE but were still identified on mammogram. Of note, one of the 4 malignant lesions found by iBE and CBE went undetected by mammography.

The four iBE-/CBE-detected malignancies ranged in size from 1.2 cm to 3.0 cm and were located between 3 cm and 6 cm from the nipple. Of these 4 detected malignancies, 3 were invasive ductal carcinomas and 1 was tubulolobular carcinoma. The three iBE-/CBE-undetected malignancies ranged in size from 0.3 cm to 1 cm and were located between 7 cm and 10 cm from the nipple in the upper outer breast. Of these 3 undetected malignancies, 2 were invasive ductal carcinomas and 1 was DCIS.

TABLE 4. CBE Versus Mammogram for Positive Exam Detection

Value	Mammogram (+)	Mammogram (–)	Measure
CBE (+)	12	54	
CBE (–)	23	397	NPV = 94.5%
Measure		Sp = 88.0%	κ = 0.16

Abbreviations: CBE, clinical breast examination; NPV, negative predictive value; Sp, specificity.

TABLE 5. Final Cohort Patient Diagnoses With Summary of Exams

Final Diagnosis	No.	Mammogram (+)	iBE (+)	CBE (+)	Ultrasound (+/–/ND)
No findings	439	2	83	45	0/11/428
Benign findings	10	7	2	4	4/0/6
Cyst	20	12	10	10	14/5/1
Fibroadenoma	7	4	1	2	2/1/4
Microcalcifications	2	2	0	0	1/0/1
Atypical hyperplasia	1	1	0	0	1/0/0
Mass	2	2	2	2	2/0/0
DCIS or breast cancer	5	5	3	3	4/0/1

Abbreviations: CBE, clinical breast examination; DCIS, ductal in situ carcinoma; iBE, intelligent Breast Exam; ND, not determined.

Figure 1 displays the entire screening population of 486 patients, including malignancy patients, superimposed on respective results for iBE, CBE, and mammogram. Of the 12 patients with positive results for iBE, CBE, and mammogram, only 3 were assigned a final diagnosis of breast cancer. The other 2 patients who were assigned a final diagnosis of DCIS or breast cancer had positive results on mammogram alone.

DISCUSSION

This study was designed to evaluate the performance of the iBE device compared with results on mammography (BI-RADS 3, 4, or 5) in a screening population. In this well-resourced US population, the specificity of iBE for predicting a negative mammogram was calculated as 80.3%. The negative predictive value in this group was 94.0%. Such results suggest the ability to reduce the population in need of additional diagnostic workup by 80% and may potentially translate into enormous cost savings for LMICs that are struggling to introduce screening programs for their at-risk populations. However, more studies in unscreened populations are needed to test this hypothesis.

Of note, the calculated κ value of 0.08 represents a negligible level of agreement between iBE and mammography. It is clear that these two testing modalities use different characteristics to screen the breast—compressibility in the case of iBE versus radiographic appearance in the case of mammography. This may contribute to the limited overlap observed between the false positive groups for mammography and iBE/CBE. For most of the true positive results in this study, however, and those of our prior studies,[14,15] mammography, ultrasound, and iBE/CBE successfully identified the clinically relevant target lesions.

However, given this minimal level of agreement between iBE and mammography, this side-by-side comparison may not represent the best assessment of the utility of iBE. Instead, when used as a triage test, iBE may improve the

TABLE 6. Characteristics of Detected Malignancies (5 patients, 7 cancers)

Patient	Breast	Pathology	Size, cm	Location	iBE Result	CBE Result	Mammogram Result	Ultrasound Result
1 (bilateral; 0028; BMI: 34.9; bra: 42C)	Right	DCIS	0.7	10 o'clock position, 7 cm from nipple	Negative	Negative	Positive	Positive
	Left	Invasive ductal carcinoma	3.0	10 o'clock position, 6 cm from nipple	Positive	Positive	Positive	Positive
2 (0138; BMI: 47.0; bra: 46C)	Right	Invasive ductal carcinoma	0.3	Upper outer posterior 11 o'clock position, 10 cm from nipple	Negative	Negative	Positive	Not done
3 (bilateral; 0256; BMI: 27.5; bra: 38C)	Right	Invasive ductal carcinoma	1.2	8 o'clock position, 4 cm from nipple	Positive	Positive	Positive	Positive
	Left	Tubulolobular carcinoma	1.7	6 o'clock position, 3 cm from nipple	Positive	Positive	Negative	Not done
4 (0285; BMI: 21.9; bra: 36E)	Right	Invasive ductal carcinoma	2.4	Retroareolar region to 6 o'clock position, 5 cm from nipple	Positive	Positive	Positive	Positive
5 (1013; BMI: 28.1; bra: 38C)	Right	Invasive ductal carcinoma	1.0	10 o'clock position, 10 cm from nipple	Negative	Negative	Positive	Positive

Abbreviations: BMI, body mass index; CBE, clinical breast examination; DCIS, ductal in situ carcinoma; iBE, intelligent Breast Exam.

subsequent performance of mammography by decreasing the pool of true negatives that are imaged. Triage in LMICs is important because widespread mammography is not financially or infrastructurally feasible.[16]

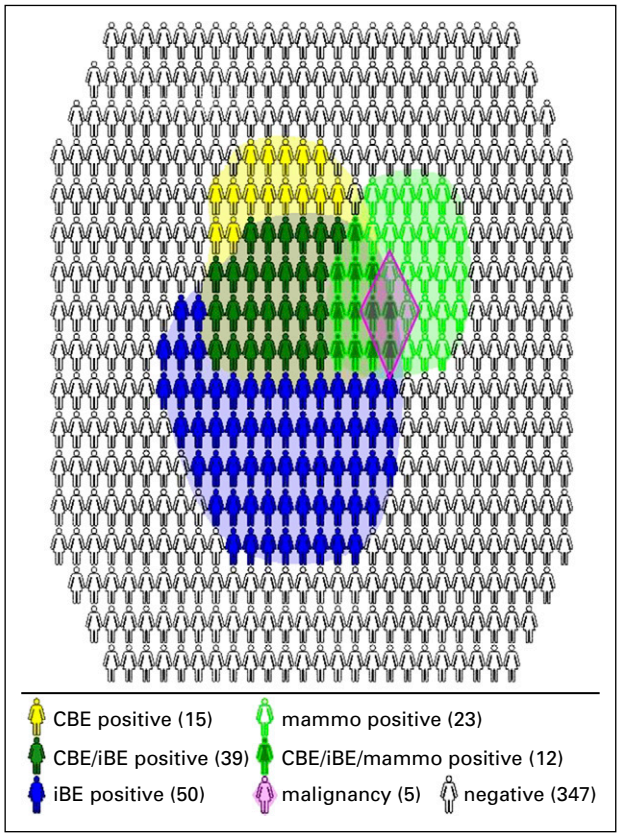

FIG 1. Positive exam cohorts within the screening population. CBE, clinical breast examination; iBE, intelligent Breast Exam.

In the CBE versus mammogram comparison, a similar result was observed with an acceptable specificity for predicting a negative mammogram of 88.0% and negative predictive value of 94.5%. The calculated κ value of 0.16 again represents a negligible agreement between these two tests. This result is in line with prior comparisons of the two test modalities[17,18].

The iBE versus CBE comparison, however, is promising in the context of a growing need for additional triage mechanisms in resource-limited settings.[16] The κ value reported a moderate level of agreement between these two tests. This indicates that iBE and CBE likely measure similar characteristics in the breast. Furthermore, iBE and CBE both demonstrated excellent negative predictive value (94% and 94.5%, respectively) compared with mammography. This result supports the use of iBE as an adjunct triage tool to reduce the number of patients referred for imaging, particularly in countries in which widespread screening mammography for all is not realistic. In this study, most iBE and CBE exams were performed by one well-trained technician. The study did not test variability in performance of iBE and CBE across multiple health care workers as would be seen in real-world implementation. A study of interoperator reliability is planned for iBE and CBE and would further support the role of iBE as a triage tool if equal or greater interoperator reliability for iBE over CBE is demonstrated.

The authors do not recommend any specific screening age. The actual facts on the ground in LMICs will dictate which populations should be screened and with which tools. On the basis of these data, the iBE tool is not ready for application as a standalone tool, but its implementation

should be studied in a more representative population and with less-experienced health care workers who are trying to acquire clinical skills promptly. The breast cancer population in LMICs is different than the patients in this Western screening cohort. In some LMICs, up to 90% of cancers are found by the patient herself. CBE has been demonstrated to be effective, but CBE is difficult to learn in LMICs because one needs to receive feedback on diagnostic workups to improve. Although it needs to be confirmed in implementation studies, the immediate feedback and result tracking with iBE is likely to be helpful for training in this respect.

Although the study cohort contained a small number of diagnosed malignancies, descriptions were included to provide a qualitative context for evaluation. iBE failed to detect three malignant lesions that ranged in size from 0.3 cm to 1.0 cm but successfully identified all others greater than that threshold. In LMICs in which the majority of women present with later-stage disease,[19,20] this threshold is an important one. Such a triage device as iBE has greater prospective utility in the LMIC setting, as opposed to high-resource countries, to aid in earlier detection of clinically significant breast cancers globally. With a 1.0-cm threshold, this device may be less likely to lead to overdiagnosis and overtreatment of clinically insignificant cancers and premalignant lesions as can be observed in well-resourced areas.

In the diagnostic workup, 5 directed ultrasounds were able to identify 5 malignant lesions; 2 lesions did not undergo initial ultrasound. Clearly, ultrasound has been shown to be a low-cost, portable diagnostic tool in resource-poor countries.[21,22] In many LMICs without the resources to emulate Western protocols, an iBE and CBE followed by a directed ultrasound could represent the most feasible route to earlier diagnosis.[23,24] This triage design is a promising area of future investigation.

Ultimately, our data suggest that there is potential for iBE and CBE to synergize as triage tools to significantly reduce the population of patients who need additional diagnostic imaging in resource-limited areas. Furthermore, CBE alone versus no screening has been demonstrated to help downstage breast cancers at presentation in LMICs.[16,25,26] Although CBE is cost effective and often serves as a crucial point of contact between women in LMICs and the health care system, participation rates are low, particularly in rural areas in which the presence of trained health care workers who are competent in CBE is limited.[27] iBE may be a strong ally in such settings, as it is easily operated by nonmedical health workers with proper training. Furthermore, its electronic platform may address one of the major barriers to improving oncologic care worldwide: the failure to connect detection methods with available resources for additional workup and treatment.[16,28] Because iBE results are electronically generated, they may allow for easier organization and geographic tracking of outreach efforts, and can serve to guide follow-up imaging with ultrasound, all of which are crucial for the success of new point-of-care technologies.[29] This potential, however, rests heavily on proper implementation, considering unique societal factors, breast health literacy, and the local health infrastructure of each LMIC instead of widespread attempts that are not tailored to existing frameworks.[30]

Although superior to the iBE device with regard to detection in high-income countries, mammography is not the most feasible early detection tool in resource-strained areas.[31,32] Instead, because the iBE device has demonstrated performance that is similar to CBE by a well-trained technician, we propose a shift of focus toward wider implementation of these early triage mechanisms. There are multiple CBE/iBE device pilot and implementation programs underway in LMICs across the globe, with more than 180,000 iBE exams performed to date. These programs can help establish the generalizability of this triage approach in multiple environments. Furthermore, additional research must investigate whether this early triage mechanism affects mortality. Clearly, detection without viable treatment channels is futile in LMICs in which a high burden of breast cancer and vast disparities in survival still exist.

In conclusion, this study demonstrated excellent negative predictive value of iBE and agreement between iBE and CBE as triage tests for the detection of clinically relevant breast lesions. These results support implementation studies of the iBE device as an adjunct to CBE and directed point-of-care ultrasound for triage of breast screening in resource-limited countries.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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