In this study, Ulaner et al report findings from their single-site, prospective diagnostic study comparing standard-of-care (SOC) imaging with 16α-18F-fluoro-17β-estradiol (FES) positron emission tomography/computed tomography (PET/CT) to stage cancer in patients with estrogen receptor (ER)-positive locally advanced breast cancer (LABC) (cohort 1) and detect recurrence in patients with suspected ER-positive BC recurrence (cohort 2). Ulaner et al assessed 124 participants, 62 in each cohort, who underwent both SOC imaging (CT bone scan or 18F-fluorodeoxyglucose [FDG] PET/CT, per clinician preference) and FES PET/CT within 2 weeks of each other without intervening therapy. Suspicious findings for distant metastases (cohort 1) or recurrent disease (cohort 2) on any scan directed a biopsy, which served as the histopathological reference standard confirming presence or absence of metastatic or recurrent BC. Of 14 metastases detected in cohort 1, SOC imaging detected 12 and FES PET/CT detected 11. Among 23 patients with recurrent disease in cohort 2, SOC detected 16, while PET detected 18. In patients with biopsy-proven lesions, both modalities detected disease in 20 of 37 confirmed lesions (54%) with a similar number of lesions detected by SOC only (8 lesions [22%]) and FES PET/CT only (9 lesions [24%]). Furthermore, FES PET/CT identified true-positive sites of disease in 29 of 30 findings (97%), while SOC detected true-positive sites in 28 of 34 findings overall (82%). Of note, there were 30 patients in the study with invasive lobular carcinoma (ILC), and 11 of these patients had biopsy-proven distant metastases or recurrent malignant neoplasm, 6 of which were detected by FES PET/CT only. Overall, SOC imaging detected 5 of 11 distant or recurrent disease sites in ILC (45%) while FES PET/CT detected 9 (82%).

To our knowledge, this well-designed and well-executed study is the largest prospective study to date assessing FES PET/CT for staging or restaging ER-positive recurrent or metastatic BC. Powered to determine a difference of 20% in detecting distant or recurrent disease, the study instead found no statistical differences for staging or restaging with SOC vs FES PET/CT in either cohort and interpreted this as equivalence of FES PET/CT to SOC for these 2 clinical indications. The results are certainly encouraging and support the utility of FES for staging and restaging in ER-positive BC and warrant further studies, including multisite trials, to support more routine use in clinical practice.

FES is an ER-binding PET tracer that accurately and noninvasively assesses whole-body ER-expression with high concordance with immunohistochemical (IHC) staining in large prospective studies. In the largest study to our knowledge, a prospective multicenter trial of 200 women with newly diagnosed metastatic ER-positive BC, FES PET/CT demonstrated a sensitivity of 95% and specificity of 80% for ER-positive metastatic disease. The earliest studies of FES PET tested it as a biomarker to estimate the likelihood of response to therapy, akin to the use of ER assay of biopsy material by IHC. In patients with ER-positive metastatic BC by IHC, lack of uptake on FES PET/CT is strongly associated with lack of response to endocrine therapy. In a 2006 study of patients with metastatic ER-positive BC by IHC, none of the 15 patients with standardized uptake value less than 1.5 on FES PET responded to subsequent endocrine therapy. Other subsequent studies reported similar findings, and further prospective studies are ongoing. FES PET/CT is therefore a single, noninvasive method that can be used to both assess whole-body ER-expression and estimate the likelihood of response to ER-targeted therapy. The Society of Nuclear Medicine and Molecular Imaging Appropriate Use Criteria for FES PET/CT indicate FES PET/CT is appropriate in patients with recurrent...
or metastatic ER-positive BC to assess ER status of lesions that are difficult to biopsy or when biopsy is not diagnostic, assess ER-status of lesions that are equivocal or suspicious on other imaging studies, and when considering first- or next-line endocrine therapy.5

The use of FES PET/CT for the detection of ER-expressing BC, specifically staging and restaging, has been somewhat less studied. The Society of Nuclear Medicine and Molecular Imaging guidelines state that FES PET/CT may be appropriate for staging ILC and low-grade invasive ductal carcinoma or restaging patients with suspected recurrence but suggest that more data are needed to determine utility and accuracy. This is the focus of the study by Ulaner et al,1 which adds important data for this indication. ILC is a subtype of BC that is typically ER-positive and notoriously difficult to detect on imaging because it tends to grow in an infiltrative, less cohesive way.6 ILC can be occult on mammography, ultrasonography, breast magnetic resonance imaging, and even FDG PET/CT (due to low glucose metabolism and therefore lower standardized uptake values). The poorer performance of FDG PET/CT in the ILC population, and the typical high ER expression of ILC, have motivated multiple investigations of FES PET/CT in this BC subtype.

In a prior study by Ulaner et al7 reviewing 6 prospective trials of patients with metastatic BC at a single institution, 7 patients were identified with ILC who had FES and FDG PET/CTs performed within 5 weeks of each other and without intervening change in management. The 2 PET agents compared favorably in these 7 patients, with FES PET/CT identifying more metastatic lesions than FDG PET/CT in 5 patients.7 One patient had disease only detected on FES PET/CT, and no patients had disease only detected on FDG PET/CT, although 1 patient had FDG-avid liver metastases that were not seen on FES PET/CT.7 This new study by Ulaner et al1 builds on these preliminary data and again suggests particular utility of FES PET/CT in patients with ILC. Other PET agents, such as 68Ga-fibroblast activation protein inhibitor ([68Ga]FAPI) and 18F-fluciclovine, are also currently being investigated for use in ILC and have also shown some early promising results.

While this study by Ulaner et al1 points to the utility of FES PET/CT for staging ER-positive BC, there are some remaining questions to be addressed. Ulaner et al1 concluded equivalent performance for FES PET/CT and SOC, but the study was powered to identify a 20% improvement in detection for FES PET/CT vs SOC. The results of the study by Ulaner et al1 suggest that FES PET/CT and SOC are complementary, with approximately 50% of lesions detected by either SOC only or FES PET/CT only. Further guidance for how to choose patients for SOC (including possible FDG PET/CT) vs FES PET/CT would be helpful. One important limitation to staging and restaging with FES PET/CT is the high uptake in the liver, the site of steroid metabolism, which severely limits the detection of liver metastases, a common site of metastatic BC. Conversely, one might surmise that low-grade ER-positive lesions, which tend to have low FDG uptake, might be better suited to FES PET/CT; however, the study by Ulaner et al1 included a only small number of grade I cancers, in which FES PET/CT would likely have shown improved performance over FDG PET/CT. These are questions that should be addressed in future studies.

From another perspective, the study by Ulaner1 provides some hints that FES and FDG PET/CT might be complementary. Metastatic BC of all types can be spatially and/or temporally heterogeneous, with variable FDG and FES uptake. Studies suggest that FDG and FES PET/CTs demonstrate different, and complementary, information to improve prognosis and optimize treatment decisions in patients with BC and that paired FDG and FES PET/CT is important to identify disease sites without FES uptake that may indicate a loss of ER expression, important in choosing treatment. A study by Kurland et al8 prospectively assessed FDG and FES uptake in 84 patients prior to endocrine therapy for primary, recurrent, or metastatic BC and found that the pattern of FDG and FES findings was associated with outcomes, with the longest median progression-free survival (PFS) in patients with low FDG-avid disease (26.1 months), intermediate PFS in patients whose disease demonstrated high FDG uptake and concomitant high FES uptake (7.9 months), and shortest PFS in patients whose disease demonstrated high FDG uptake and low FES uptake (3.3 months).8 Combined FDG and FES imaging may also alleviate the limited liver evaluation of FES-only imaging, since liver metastases can be well seen on FDG PET/CT. Rather than identifying a single optimal PET
study for BC staging and restaging, additional research might continue to support the effectiveness of dual-tracer staging and restaging, which may be feasible with improvements in PET imaging technology.

Overall, this study by Ulaner et al contributes important data to guide the use of new molecular imaging tools for BC diagnosis and staging, contributing to the overall goal of precision breast oncology. Their results add to prior data supporting a role for FES PET/CT in staging LABC and metastatic BC, particularly in the ILC population, and warrant additional studies to further investigate these, and other, indications for FES PET/CT and further studies of dual FES and FDG PET/CT.

REFERENCES