^{18}F-FES Whole-Body Imaging Protocol for Evaluating Tumor Estrogen Receptor Status in Patients with Recurrent or Metastatic Breast Cancer

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In September 2020, the *Journal of Nuclear Medicine and Technology* published a continuing education article, "Breast Cancer: Evaluating Tumor Estrogen Receptor Status with Molecular Imaging to Increase Response to Therapy and Improve Patient Outcomes," that reviewed a promising new PET tracer, 16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES). This tracer had the potential to be a valuable tool for medical oncologists and breast surgeons in noninvasively evaluating the estrogen receptor site status of their patients' recurrent tumor and secondary metastatic lesions. In May 2020, ^{18}F-FES received Food and Drug Administration approval and began being marketed by Zionexa using the trade name Cerianna and manufactured by PETNET. In May 2021, GE Healthcare acquired Zionexa, and Cerianna and is now being marketed by GE Healthcare and is still being manufactured by PETNET. This article will review the ^{18}F-FES package insert information and imaging protocol, as well as important guidelines for imaging with ^{18}F-FES.

Key Words: breast cancer; estrogen receptor imaging; ^{18}F-fluoroestradiol; Cerianna; ^{18}F-fluoroestradiol; patient outcomes

J Nucl Med Technol 2023; 51:188–193
DOI: 10.2967/jnmt.122.265272

Sometimes breast cancer patients present their medical oncologist or breast surgeon with a clinical dilemma on how their particular type of cancer should be treated, especially when standard treatment options fail. An accurate diagnosis and treatment plan remain essential for patient survival and longevity. Some breast cancer tumors respond to treatment, whereas others do not. Knowing the type of breast tumor, its estrogen receptor (ER) site status, and how it might respond to therapy is vital to effective and successful treatment, ultimately improving patient outcomes and overall survival rates.

An accurate and high-quality 16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES) (Cerianna; Zionexa) whole-body (WB) scan can be a key piece of the diagnostic workup for the physician. ER-positive (ER+) tumors are the most prevalent breast tumor type, representing approximately 75%–80% of all breast tumors (*1*), making ^{18}F-FES WB imaging a diagnostic tool that can help accurately identify ER+ tumor cells throughout the body. ^{18}F-FES WB imaging noninvasively evaluates the ER status of patients with recurrent or metastatic breast cancer. It is essential to be aware of the ^{18}F-FES package insert (PI) and contraindications and follow the correct preparation for the scan to ensure the highest-quality images possible.

MECHANISM OF ACTION, PHARMACODYNAMICS, AND PHARMACOKINETICS

^{18}F-FES has a 60%–100% relative binding affinity for the ER, making it an excellent tracer to image ERs throughout the body (*2*). The pharmacodynamics of ^{18}F-FES uptake are directly proportional to tumor ER expression measured by in vitro assays: the higher the ER+ expression, the greater the uptake, and vice versa (*3*). According to the ^{18}F-FES PI, the relationship between plasma concentrations and image interpretation has not been studied (*3*).

^{18}F-FES is rapidly metabolized in the liver, and at 20 min after injection, approximately 20% of circulating radioactivity in the plasma is in the form of nonmetabolized ^{18}F-FES. At 120 min after injection, less than 5% of the injected dose remains unmetabolized (*3*).

According to section 12.3 of the PI, 95% of ^{18}F-FES is bound to plasma proteins after intravenous injection, and the tracer distributes primarily within the hepatobiliary system but also within the small and large intestines, heart wall, blood, kidney, uterus, and bladder. The critical organ is the liver, which receives 0.126 mGy/MBq (*3*). ^{18}F-FES is also distributed systemically, with high physiologic uptake in the

Received Nov. 30, 2022; revision accepted Apr. 25, 2023.
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Published online Jul. 11, 2023.
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uterus and ovaries (*2*). The effective radiation dose resulting from an administration of 222 MBq (6 mCi) to an adult weighing 70 kg is estimated to be 4.9 mSv (*3*). Excretion is biliary and urinary (*3*).

PATIENT SELECTION

Physicians must keep several things in mind when selecting the right treatment options. The hormone receptor status in the primary tumor does not necessarily predict the hormone receptor status of metastatic lesions. A primary tumor may be heterotypical, having both ER+ and ER-negative receptors within the lesion instead of a single ER status type. Hormone receptor genes may be downregulated or lost in metastatic lesions (*4*), complicating accurate treatment decision-making. So, one treatment option might work for the ER+ primary tumor but not for a metastatic lesion whose receptor has become downregulated or lost and is now ER-negative. Lindstrom et al. noted that in about a third of patients, ER status can change after disease recurrence or progression and that a change to ER-negative was associated with a 48% increase in mortality (*4*). The ability to predict therapeutic response in distant lesions is critical to planning the approach to treating patients with metastatic disease, and ^{18}F-FES ER imaging is like getting a noninvasive WB biopsy in which all ER+ lesions throughout the body can be visualized on the scan. Most importantly, ^{18}F-FES ER imaging correlates well with immunohistochemistry results and may be able to predict response to endocrine therapy (*5,6*). Patients initially diagnosed with lobular breast cancer who are being worked up for recurrent or metastatic breast cancer are perfect candidates for ^{18}F-FES WB imaging because lobular breast cancer tumors have a low affinity for ^{18}F-FDG but a high affinity for ^{18}F-FES. Figures 1 and 2 illustrate 2 patients with lobular breast cancer. ^{18}F-FDG scans showed uptake in some tumors, but when patients 1 and 2 were scanned with ^{18}F-FES at 1 d and 1 mo, respectively, after ^{18}F-FDG PET, the ^{18}F-FES scans showed multiple lesions not seen on the ^{18}F-FDG PET scans.

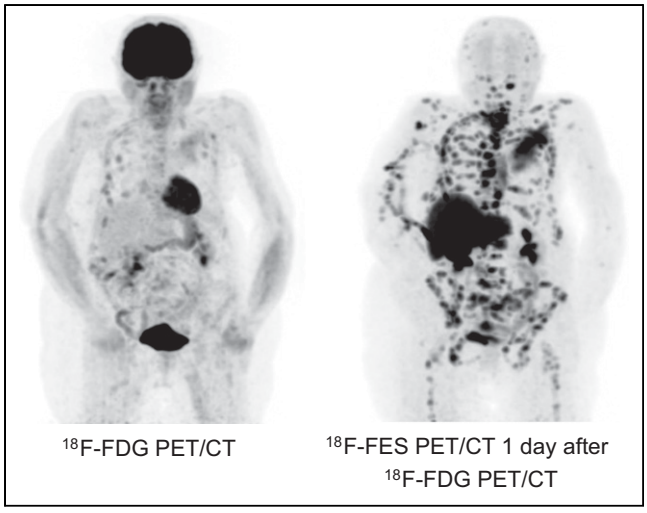

FIGURE 1. Patient 1. History: ER+, HER2-negative, T2N0M0 left breast lobular carcinoma treated with neoadjuvant chemotherapy, surgery, adjuvant chemotherapy, radiation therapy, and 5 y of hormone therapy (tamoxifen). Eight years after treatment completion, T10 and T12 fractures emerged, and cancer antigen 15-3 was 3,500 U/mL (reference level, <25 U/mL). Outcome: all lesions expressed ERs on ^{18}F-FES PET/CT. Accumulation was higher for ^{18}F-FES than for ^{18}F-FDG, probably because of lobular histology. Some lesions were barely seen with ^{18}F-FDG. Treatment: aromatase inhibitor (exemestane), with lesion stabilization and cancer antigen 15-3 reduction from 3,500 to 1,50 U/mL 2 y after treatment began. (Reprinted from (*10*).)

APPROPRIATE-USE CRITERIA FOR ER-TARGETED PET

In October 2022, the appropriate-use criteria for ER-targeted PET imaging with ^{18}F-FES were created to help medical oncologists, breast surgeons, and interpreting physicians know when to order or not order ER-targeted PET imaging. The working group of experts determined that ordering ^{18}F-FES PET imaging is appropriate in 3 instances: to assess for ER functionality when endocrine therapy is considered either at initial diagnosis of metastatic breast cancer or after progression of disease on endocrine therapy, to assess the ER status of lesions that are difficult or dangerous to biopsy, and to assess the ER status of lesions when other tests are inconclusive (*7*).

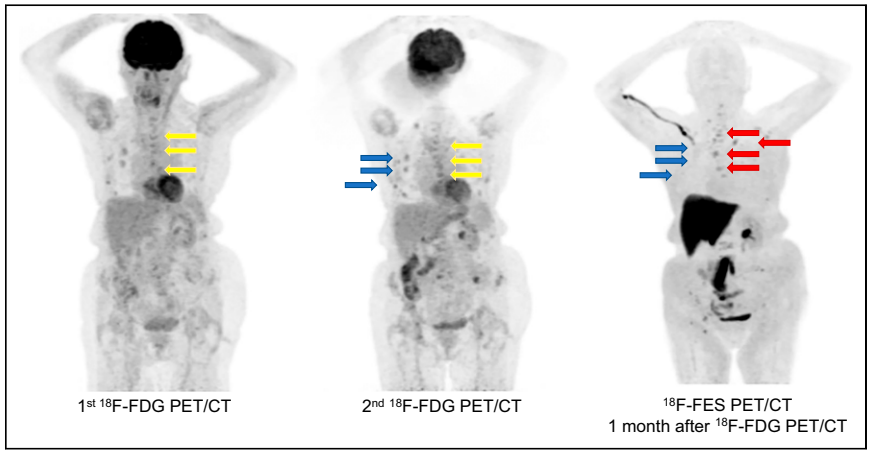

FIGURE 2. Patient 2. History: ER+, progesterone receptor–negative, HER2-negative lobular carcinoma with initial bone metastases. Outcome: lesion heterogeneity (^{18}F-FES PET/CT scan showing both ^{18}F-FES–positive lesions [red arrows] and ^{18}F-FES–negative lesions [blue arrows]). No uptake was seen on ^{18}F-FES PET/CT scan for lesions that showed uptake on second ^{18}F-FDG PET/CT scan (blue arrows). ^{18}F-FES–positive lesions corresponded to progressive lesions seen with ^{18}F-FDG (yellow arrows), potentially explaining progression with hormone therapy. Treatment: aromatase inhibitor (blocks ERs), which resulted in reduction or disappearance of ^{18}F-FES PET signal; radiation therapy on T9 and left iliac bone; and exemestane, resulting in bone progression on L5 and left iliac bone. (Reprinted from (*10*).)

TABLE 1
Appropriate-Use Guidelines for 14 Clinical Scenarios (*7*) in Which ^{18}F-FES PET Might Be Used

Scenario	Appropriateness of use	Score
	Appropriate (scores of 7–9)	
8	For assessing ER status when lesions are difficult to biopsy or biopsy is nondiagnostic	8
9	For considering second line of endocrine therapy after progression of metastatic disease	8
10	For considering endocrine therapy at initial diagnosis of metastatic disease	8
14	For detecting ER status when findings of other imaging tests are equivocal or suggestive	8
	May be appropriate (scores of 4–6)	
2	For diagnosing malignancy of unknown primary when biopsy is nonfeasible or nondiagnostic	5
5	For routine staging of extraaxillary nodes and distant metastases	5
6	For staging invasive lobular carcinoma and low-grade invasive ductal carcinoma	5
7	For assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy	5
13	For detecting lesions in suspected or known recurrent or metastatic breast cancer	5
	Rarely appropriate (scores of 1–3)	
1	For diagnosing primary breast cancer	2
3	For routine staging of primary tumor (T staging)	1
4	For routine staging of axillary nodes	3
11	For considering endocrine therapy at initial diagnosis of primary breast cancer	1
12	For measuring response to therapy	1

Inappropriate-use criteria must also be reviewed to make sure physicians are not ordering scans for patients who will not benefit. Ordering a ^{18}F-FES scan inappropriately results in unnecessary radiation exposure to the patient, increased out-of-pocket costs to the patient, and unnecessary costs to the patient's insurance company. The working group came up with 14 clinical scenarios in which ^{18}F-FES PET imaging could be used, grouping the scenarios as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores of 7–9 indicate that the procedure is appropriate for the scenario and is generally considered acceptable. Scores of 4–6 indicate that the procedure may be appropriate for the scenario; this implies that more evidence is needed to classify the scenario definitively. Scores of 1–3 indicate that the procedure is rarely appropriate for the scenario and is generally not considered acceptable (*7*). Table 1 outlines the scenarios and their scores.

CLINICAL INDICATION AND LIMITATIONS OF USE

^{18}F-FES PET is indicated for detecting ER+ lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer (*3*). The ^{18}F-FES limitations of use state that "Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. CERIANNA is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR)" (*3*).

PATIENT PREPARATION

The patient should be well hydrated before being injected. If a patient is of childbearing age, it is recommended that pregnancy status be checked per instruction guidelines. The ^{18}F-FES PI states that "Certain classes of systemic endocrine therapies, including ER modulators and ER downregulators, block ER, reduce the uptake of fluoroestradiol F 18, and may reduce detection of ER-positive lesions after administration of CERIANNA. Drugs from these classes such as tamoxifen and fulvestrant may block ER for up to 8 and 28 weeks, respectively. Do not delay indicated therapy to administer CERIANNA. Administer CERIANNA prior to starting systemic endocrine therapies that block ER" (*3*).

TABLE 2
^{18}F-FES Acquisition Parameters

Acquisition parameter	Specification	Standard/preferred/optional
PET scanner type	2 or 3 dimensional	Standard
Energy peak	511 keV	Standard
Energy window	^{18}F-fluorine	Standard
Patient position	Supine with arms above head, if possible	Standard
Injection-to-scan time	20–80 min after injection	Standard
	80 min	Preferred
Acquisition area	WB (thighs to vertex)	Standard
Acquisition time	20–30 min	Standard
Number of bed positions	6–8	Standard
Time per bed position	3–4 min	Standard

Additional information to keep in mind when imaging with ^{18}F-FES is that lower estrogen levels will result in no or low uptake of ^{18}F-FES (*8*). Aromatase inhibitors and the hormone therapy medication mentioned above block ERs and may reduce or eliminate the ^{18}F-FES PET signal (*8*).

There are no contraindications before performing a ^{18}F-FES scan (*3*); however, knowing when other recent nuclear medicine studies have been performed (radiopharmaceutical-dependent) can be helpful to ensure the highest-quality ^{18}F-FES PET scan with no interference from any other radiopharmaceutical.

DOSE AND ADMINISTRATION

The recommended dose of ^{18}F-FES is 222 MBq (6 mCi), with an acceptable dose range of 111–222 MBq (3–6 mCi). ^{18}F-FES is intravenously injected over a 1- to 2-min time frame followed by a 0.9% sodium chloride flush to ensure proper dose delivery (*2*). It is preferred that ^{18}F-FES be injected in an arm contralateral to the primary tumor site (*2*). The ^{18}F-FES user guide "Seeing ClearER+" states, "Administering Cerianna through a central port is not contraindicated but is dissuaded" (*2*). ^{18}F-FES may be diluted with 0.9% sodium chloride injection (*3*). Because ^{18}F-FES imaging can begin anywhere from 20 to 80 min after injection (*3*), PET imaging departments can pick a postinjection scan time that best fits the department's workflow. If most scans in the department are done at 45 min or 60 min after injection, then acquiring a ^{18}F-FES scan at 45 or 60 min after injection is fine and is still follows the PI guidelines for imaging; however, scanning 80 min after injection is preferred (*3*).

Because ^{18}F-FES is not glucose-dependent, light, noise, and sound will not affect uptake after tracer injection. Physical activity before a ^{18}F-FES injection does not need to be avoided as it does for ^{18}F-FDG. After ^{18}F-FES is injected, as with all PET procedures, hydration and frequent voiding by the patient are suggested to help decrease radiation exposure. Physical activity is permitted after ^{18}F-FES injection (*2*). Sedation can be given if needed before imaging, but patients should not be allowed to drive themselves home afterward.

ACQUISITION AND PROCESSING PARAMETERS

The acquisition and processing parameters for ^{18}F-FES WB PET are fairly simple. The standard WB ^{18}F-FDG acquisition protocol can be used for acquiring a WB ^{18}F-FES scan. The first steps include cloning the existing ^{18}F-FDG protocol and adding ^{18}F-FES to the isotope inventory. Once ^{18}F-FES is loaded into the isotope inventory, it is selected from the available isotopes and the imaging protocol is resaved as ^{18}F-FES WB PET. With older PET scanners, it is important to increase the time per bed position by 30% (i.e., 3 min to 4 min or 5 min to 6.5 min) to acquire an adequate number of counts per bed position and ensure a good-quality scan. For PET/CT protocols, the manufacturer's recommendations for CT acquisition parameters should be followed (*2,3*). Table 2 outlines other important acquisition settings, including PET scanner type, energy peak and energy window, preferred patient positioning, injection-to-scan time, and acquisition area. Preferred acquisition times, number of bed positions, and time per bed position are also listed.

Other important acquisition steps for a ^{18}F-FES WB PET scan are to have the patient void before scanning, to position the patient supine on the imaging table with arms above head if possible, and to scan from vertex to mid thigh or knees (*2*). Once the scan is complete, it is also important to review the raw data for image quality and motion or any other defects that may require additional follow-up. If significant motion is detected, making a scan unreadable, the scan should be repeated.

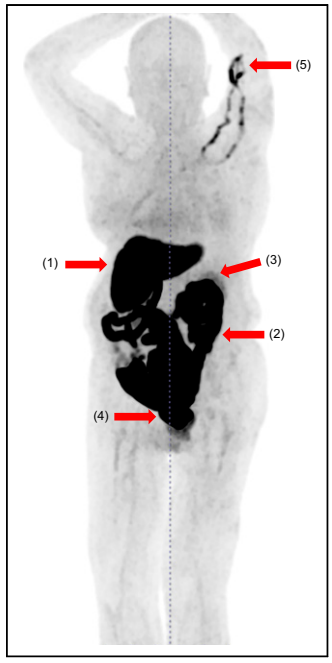

FIGURE 3. Normal increased uptake of ^{18}F-FES in liver (1), gastrointestinal tract (2), kidneys (3), urinary bladder (4), and injected vessel (5). Uptake in injected vessel, seen in most patients, is probably due to sticking of tracer to vessel wall or endothelial cells (*2*). (Courtesy of DRA Imaging.)

It is recommended that processing of ^{18}F-FES WB PET scans follow the Society of Nuclear Medicine and Molecular Imaging procedure standards for ^{18}F-FDG PET/CT (*2*).

^{18}F-FES TRACER DISTRIBUTION PATTERNS

Normal uptake of ^{18}F-FES can be seen in the liver, gastrointestinal tract, kidneys, and urinary bladder (Fig. 3) (*2*). Increased uptake may also be seen in the injected vessel in most patients; the cause is unknown but is probably due to sticking of the tracer to the vessel wall or endothelial cells. If the uptake appears abnormal or questionable, the interpreting physician should be informed and should determine whether additional images are needed (e.g., a skull image illustrating 2 metastatic brain lesions is shown in Fig. 4).

IMAGE INTERPRETATION

Although training is not required for ^{18}F-FES interpreters, it is strongly suggested. Information on training can be obtained through a Cerianna sales representative or the GE Healthcare website (https://landing1.gehealthcare.com/PDX-US-Cerianna-InterpreterTraining.html).

According to the ^{18}F-FES user's guide, in interpretation of an ^{18}F-FES WB scan, "Detection of ER+ tumors should be based on comparison with tissue background outside of organs with high physiologic uptake and regions with high

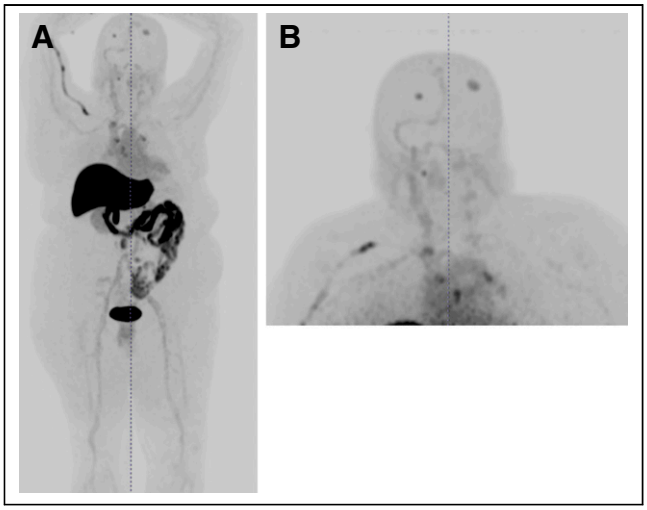

FIGURE 4. Abnormal uptake of ^{18}F-FES. Although ^{18}F-FDG WB imaging is not helpful in visualizing brain metastasis, ^{18}F-FES WB imaging is. (A) WB ^{18}F-FES image from vertex to mid thighs, with increased uptake in chest and brain. (B) Extra image of skull that clearly illustrates the 2 brain metastatic lesions (*2*). (Courtesy of DRA Imaging.)

activity due to hepatobiliary and urinary excretion. As a general rule, all lesions with fluoroestradiol F 18 uptake greater than background (e.g., physiological liver uptake) are considered ER+". Assessing ER expression in regions with normally high physiologic activity (e.g., liver) is not advised (*2*).

WARNINGS, PRECAUTIONS, AND ADVERSE REACTIONS

Several sections of the ^{18}F-FES PI should be reviewed carefully, including the warnings and precautions (section 5) and the adverse reactions (section 6). The former includes a risk of misdiagnosis regarding inadequate tumor characterization and other ER+ pathology, stating, "Breast cancer may be heterogeneous within patients and across time. CERIANNA images ER and is not useful for imaging other receptors such as HER2 and PR. The uptake of fluoroestradiol F 18 is not specific for breast cancer and may occur in a variety of ER-positive tumors that arise outside of the breast, including from the uterus and ovaries. Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer" (*3*). Another risk of misdiagnosis regards false-negative ^{18}F-FES findings. Negative ^{18}F-FES findings do not rule out ER+ breast cancer. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over discordantly negative ^{18}F-FES findings (*3*).

Regarding adverse reactions, the most common in over 1,200 injections during clinical trials were injection-site pain and dysgeusia (distortion of taste), occurring in less than 1% of patients (*3*).

USE IN SPECIAL PATIENT POPULATIONS

Use of ^{18}F-FES in specific patient populations is also important to review. According to the PI (*3*), pregnant woman should be advised of the potential risks of fetal exposure to radiation doses, and lactating women should be advised to avoid breastfeeding for 4 h after administration. Regarding geriatric use, clinical studies did not reveal any difference in pharmacokinetics or biodistribution in patients aged 65 y or over.

BENEFITS OF ^{18}F-FES ER IMAGING

There are many benefits to imaging with ^{18}F-FES; WB imaging can be used when lesions are inaccessible or challenging to biopsy or when lesions are insufficiently suggestive to justify an invasive procedure. ^{18}F-FES imaging is also beneficial when the tumor pathology is aggressive or a patient refuses biopsy. ^{18}F-FES imaging can also evaluate potential disease heterogeneity. A study by Yang et al. showed that 37.5% of patients with metastatic breast cancer had a heterogeneous pattern of both ER+ and ER-negative lesions (*6*). Evaluating all lesions for their ER status is a critical step in determining the appropriate treatment option, helping improve the overall response to therapy, the patient's outcome, and the patient's ultimate survival. Breast imaging with ^{18}F-FES can complement a patient's biopsy and can noninvasively evaluate multiple areas of the body, including organs such as the brain, which standard ^{18}F-FDG WB imaging cannot do.

Although ^{18}F-FES imaging has many benefits, it does have some limitations. It has a limited ability to detect liver metastases because it has increased uptake in the liver due

TABLE 3
^{18}F-FES Access Support

Category	Reimbursement service
Investigation of benefits	Aid in determining patient's health insurance coverage
Billing and coding assistance	Provide guidance for billing and coding requirements
Claims assistance	Help in navigating through claims process
Preservice and postservice appeals	Aid in assisting with and expediting these appeals
Prior-authorization support and status monitoring	Help with initiating and monitoring prior-authorization requests from insurance companies (prefill request on your behalf)
Medical necessity support	Provide support to establish medical necessity
Peer-to-peer preparation	Provide one-on-one collaborative training and strategies to assist health-care provider in seeking ^{18}F-FES insurance coverage

to increased hepatic metabolism (*5*). Considerable enterohepatic circulation can also complicate abdominal imaging when using ^{18}F-FES (*5*). ^{18}F-FES is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 and the progesterone receptor.

From a sensitivity and specificity perspective, ^{18}F-FES has a high accuracy for the detection of ER+ lesions, with proven concordance when compared with biopsy immunohistochemistry for determining ER status in metastatic breast cancer. The sensitivity of ^{18}F-FES is 78% (95% CR, 65.0%–88.0%), and its specificity is 98% (95% CR, 65.0%–100%) (*2*). When evaluated for efficacy for assessing the ER status of non–primary breast cancer lesions, ^{18}F-FES WB PET/CT interpretation and biopsy resulted in a 76.6% positive agreement (95% CR, 62.0%–87.7%; $P = 0.0018$) and a 100% negative agreement (95% CR, 90.8%–100%; $P = 0.00053$) (*2*).

SUPPORT WITH ^{18}F-FES ACCESS

Sometimes when a radiopharmaceutical is newly approved by the Food and Drug Administration, it can be challenging to make sure an imaging facility gets reimbursed properly by Medicare and private insurance companies. When first imaging with ^{18}F-FES, an imaging center and its billing department must confirm that they have all the billing and coding information, prior-authorization information, and any other information needed for insurance companies to correctly process the claim.

To help, GE Healthcare has created a network of reimbursement services and support ranging from benefits investigation support (determining a patient's insurance coverage) to medical necessity support (Table 3). Requesting support requires submission of a Cerianna Support Provider Consent Form signed by the physician or provider (available by calling 833-946-6392 or visiting www.cerianna.com/reimbursement) (*9*).

CONCLUSION

Since the Food and Drug Administration approved ^{18}F-FES in May 2020, ER imaging with ^{18}F-FES is now a viable option to obtain valuable information on the ER status of all tumors in the body. A single noninvasive scan can simultaneously evaluate both the primary breast tumor and any metastatic lesions—like performing a WB biopsy regarding ER status. A patient's ER status can change after metastasis occurs, resulting in a treatment option that works for the primary tumor but not for the metastases. Knowing the ER status of all tumors is vital to the success of treatment selection, especially when standard treatment options fail. Physicians need to consider the appropriate-use criteria for ^{18}F-FES to ensure that the right patient is scanned for the right reason at the right time, and PET imaging departments need to follow the PI and imaging protocol to ensure the highest-quality ^{18}F-FES WB scans possible.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

I thank Deepak Behera, MD, and Darcy Phillips for helping me with the manuscript, and I thank Ula Thompsett from DRA Imaging, Poughkeepsie, NY, for providing ^{18}F-FES images for this article.

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