Appropriate Use Criteria for Estrogen Receptor-Targeted PET Imaging with 16α-^{18}F-Fluoro-17β-Fluoroestradiol

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Executive Summary

Positron emission tomography (PET) imaging with 16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES), a radiolabeled form of estradiol, allows whole-body, noninvasive evaluation of estrogen receptor (ER). ^{18}F-FES is approved by the United States Food and Drug Administration (US FDA) as a diagnostic agent "for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer." The Society of Nuclear Medicine and Molecular Imaging (SNMMI) convened an expert workgroup to comprehensively review the published literature for ^{18}F-FES PET in patients with ER-positive breast cancer and establish appropriate use criteria (AUC) for ^{18}F-FES PET. These AUC summarize the findings and discussions of the SNMMI ^{18}F-FES workgroup. Of the clinical scenarios evaluated, the workgroup concluded that the most appropriate uses of ^{18}F-FES PET are as follows: 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 ER status of lesions that are difficult or dangerous to biopsy, and to assess ER status in lesions when other tests are inconclusive. The workgroup members hope this document will enable appropriate clinical use of ^{18}F-FES PET and more efficient approval of FES use by payers and will promote investigation into areas requiring further research.

Introduction

Breast cancer is the most common non-cutaneous cancer diagnosis in women, with nearly 300,000 new cases and over 40,000 deaths annually in the United States alone (*1*). Worldwide, there were 2.3 million new breast cancer cases in 2020, making it the most commonly diagnosed cancer globally (*2*). Estrogen receptor (ER) is highly expressed in 70%–80% of breast cancers (*3-5*). Determination of ER status is of critical importance in the management of patients with breast cancer, as it has value as both a prognostic (distinguishes tumors with a favorable prognosis from those with a poorer prognosis) and a predictive (proffers effective therapy) biomarker (*4,6-10*).

Currently, ER status is routinely determined by immunohistochemistry (IHC) of tissue samples (*11*). However, tissue sampling has several limitations. A biopsy is invasive, and the location of a lesion may make the biopsy difficult (*10*). ER expression may vary spatially from lesion to lesion and may vary over time, possibly under the selective pressure of ER-targeted therapy (*9,10,12-17*). This spatial and temporal heterogeneity in ER expression may cause results obtained from one or a few tissue samples to incompletely represent the entire ER receptor distribution in the patient tumor burden, leading to suboptimal treatment decisions. In addition, the presence of ER by IHC may not ensure that ER plays a role in tumor growth, as ER may be present but not functional for binding and/or tumor growth (*18*). Not all tumors that are ER-positive by IHC respond to ER-targeted therapy (*18,19*). Given the limitations of assessing ER status through limited tumor tissue sampling, there is a need for alternative methods for evaluation of ER status.

16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES) is a radiolabeled form of estrogen that binds to ER. Positron emission tomography (PET) imaging with ^{18}F-FES allows noninvasive identification of functional ER distribution (*18,19*). ^{18}F-FES uptake measured by PET correlates with ER IHC (*9,20-25*), successfully demonstrates ER heterogeneity within individual patients (*13-15,26,27*), serves as a prognostic biomarker (*17,27-29*), provides high diagnostic accuracy for the detection of ER-positive metastases (*9,10,19,23,25,30-32*), and can assess the efficacy of ER blockade (*33-36*). In a meta-analysis by Kurland et al. (*10*) in 2020, ^{18}F-FES PET demonstrated a sensitivity of 78% (95% confidence interval 65%–88%) and a specificity of 98% (65%–100%) for detection of ER-positive metastases using ER IHC as the reference standard. The largest trial of the diagnostic accuracy of ^{18}F-FES included 200 patients and was published in 2022 by van Geel et al. (*32*), demonstrating a positive predictive value for ^{18}F-FES PET of 90% (83%–94%) and a negative predictive value of 71% (55%–83%), with ER IHC as the reference standard. Regulatory agencies have approved ^{18}F-FES for imaging ER in multiple countries, including France, South Korea, and the United States. In May 2020, the United States Food and Drug Administration (US FDA) approved ^{18}F-FES as a diagnostic agent "for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer" (*37*).

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) are currently developing a Procedure Standard (Procedure Guideline) describing best practice for ^{18}F-FES PET administration and imaging, which is outside the scope of this work.

It is important to emphasize that ^{18}F-FES PET is a unique and independent imaging test from ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG PET); thus, clinical scenarios for using ^{18}F-FES

may differ from or may be an adjunct to indications for ^{18}F-FDG imaging. The purpose of these appropriate use criteria (AUC) for ^{18}F-FES PET is to provide expert opinion on clinical scenarios in which ^{18}F-FES PET will have an impact on the management of patients with ER-positive breast cancer.

Safety and Dosimetry of ^{18}F-FES PET

As the mass dose of ^{18}F-FES administered for PET imaging is sub-pharmacologic, ^{18}F-FES has an excellent safety profile with few known adverse events and no known serious adverse events. Rare side effects from ^{18}F-FES administration, affecting less than 1% of patients, include pain at the injection site and short-term dysgeusia (*37*).

As ^{18}F-FES is a radioactive molecule, it must be handled in such a manner as to protect patients and health care workers from unintended exposure. Pregnant women should be advised of the potential risk of fetal exposure. Breastfeeding should be discontinued for 4 hours after ^{18}F-FES administration (*37*). Milk can be pumped and stored during the discontinuation period for future use as per the guidelines of the Advisory Committee on Medical Uses of Isotopes (*38*).

The dosimetry for ^{18}F-FES is comparable to that of other radiotracers in terms of whole-body exposure (Table 1) (*39*). ^{18}F-FES has a calculated effective dose of 0.022 mSv/MBq, equal to 4.07 mSv for a 185 MBq (5 mCi) injected dose, with the highest uptake organ being the liver at 0.13 mSv/MBq.

Limitations of ^{18}F-FES PET

As with any imaging modality, the absence of ^{18}F-FES avidity does not necessarily equal absence of tumor. ^{18}F-FES detects ER that is functional for ligand binding (*18*). ER-negative

breast cancers and most malignancies that arise from other body sites are unlikely to be detected on ^{18}F-FES PET. Some breast cancers that are ER-positive on IHC may not express ligand-binding ER and thus will not be apparent on ^{18}F-FES PET (*10,18*).

There are both physiologic and pathologic sources of ^{18}F-FES uptake that do not represent ER-positive breast cancer. Excretion of ^{18}F-FES through the liver makes PET evaluation of this organ more difficult (*10*), but still possible (*40*). Physiologic ER may be visualized in the endometrium, myometrium, and ovary (*41*). Areas of lung that underwent radiation may demonstrate FES avidity (*42,43*). Benign neoplasms that express ER and may be ^{18}F-FES avid include meningiomas and uterine leiomyomas (*44,45*). Malignancies other than breast cancer that may be ^{18}F-FES-avid include endometrial cancer, ovarian cancer, and leiomyosarcoma (*46-49*).

Methodology

Workgroup Selection

The experts of the ^{18}F-FES AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health care providers and researchers with substantive knowledge of breast cancer and breast cancer imaging. In addition to SNMMI members, representatives from the American College of Nuclear Medicine (ACNM), the Korean Society of Nuclear Medicine (KSNM), and the Lobular Breast Cancer Society (LBCA) were included in the workgroup. Twelve members participated and contributed to the resulting AUC. A complete list of workgroup participants can be found in Appendix A. Appendix B is a summary of definitions of

terms and acronyms, and Appendix C provides the disclosures and conflicts of interest statements from all workgroup members.

AUC Development

The process for developing the AUC for ^{18}F-FES PET in patients with ER-positive breast cancer was modeled after the RAND/UCLA Appropriateness Method (*55*,*56*) and included the development of a list of common clinical scenarios encountered in the management of patients with breast cancer, a systematic review of evidence related to these scenarios, and the development of an appropriateness score for each scenario by using a modified Delphi process (*50*). This process strove to adhere to the standards of the Institute of Medicine of the National Academies for developing trustworthy clinical guidance (*51*). The process included a systematic synthesis of available evidence, individual and group ratings of the scenarios by using a formal consensus process, and AUC recommendations based on final group ratings and discussions.

Development of Clinical Scenarios

The scope of this workgroup was to focus on the appropriate use of ^{18}F-FES PET for the management of patients with ER-positive breast cancer. To begin this process, the workgroup discussed various potential clinical scenarios for which the use of ^{18}F-FES PET might be considered by practicing physicians. For all scenarios, the relevant populations were women and men of any age, race, or socioeconomic status with a biopsy-confirmed diagnosis of ER-positive breast cancer. Although data for men are less abundant, as breast cancer is far less common in men than in women, there are no convincing data to suggest that ^{18}F-FES PET applies differently to men; thus, the workgroup believes that these AUC should apply to men with ER-positive

breast cancer. Data are sparse for the use of ^{18}F-FES PET in other ER-positive malignancies such as endometrial cancer, ovarian cancer, and leiomyosarcoma (*46-49*), and so it is too early to recommend routine clinical use of ^{18}F-FES imaging for these diseases.

The workgroup identified 14 clinical scenarios for patients with ER-positive breast cancer for which physicians may want guidance on whether ^{18}F-FES PET would be considered appropriate. The scenarios are intended to be as representative as possible of the relevant patient population for the development of AUC. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each scenario. Another factor affecting the AUC recommendations was potential harm, including long-term harm that may be difficult to capture.

Systematic Review

The ^{18}F-FES AUC workgroup conducted a systematic review to develop a comprehensive clinical practice guideline for optimal strategies for the use of ^{18}F-FES in patients with ER-positive breast cancer. The inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) framework (*52*). Parameters for a targeted literature search were defined. Search terms are given in Appendix D. Parameters included relevant study designs, literature sources, types of reports, and prespecified inclusion and exclusion criteria for the literature identified. The protocol for this guideline was reviewed and approved by the SNMMI Guidance Oversight Committee and the US FDA. PubMed, MEDLINE, Embase, Web of Science, and Cochrane Collaboration Library electronic

databases were searched for evidence that reported on outcomes of interest, with updates in the literature through June 2022.

Rating and Scoring Process

In developing these AUC for ^{18}F-FES PET, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances the risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics" (*53*).

At the beginning of the process, workgroup members convened by teleconference to develop the initial scenarios. After allowing each member to evaluate the proposed scenarios in the context of the evidence summary (systematic literature review), the workgroup further refined its draft clinical scenarios to ensure their accuracy and facilitate consistent interpretation when scoring each scenario for appropriateness. Workgroup members then reviewed the evidence summary to assess benefits and risks of ^{18}F-FES PET for the revised scenarios and independently provided an appropriateness score for each. Next, the workgroup convened to view the mode and distribution of appropriateness scores for each scenario. Each scenario was discussed, with the final score selected by consensus among members. All members contributed to the final scores. No member was forced into consensus. After the rating process was completed, the final appropriate use scores were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method.

The workgroup scored each clinical scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores of 7–9 indicate that the use of the procedure is

appropriate for the specific scenario and is generally considered acceptable. Scores of 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This may imply that more evidence is needed to classify the scenario definitively. Scores of 1–3 indicate that the use of the procedure is rarely appropriate for the specific clinical scenario and is generally not considered acceptable. The division of these scores into 3 general levels of appropriateness is partially arbitrary and the numeric designations should be viewed as a continuum.

Clinical Scenarios and AUC Scores

It is important to emphasize that ^{18}F-FES PET is a unique imaging test that is independent from other clinically available radiotracers, such as ^{18}F-FDG PET. Each radiotracer has its own appropriate clinical scenarios for use. The selection of the appropriate radiotracer(s) for patients with breast cancer will depend on the specific clinical scenario presented. Clinical scenarios for using ^{18}F-FES PET and final AUC scores for ^{18}F-FES PET in patients with breast cancer are shown in Table 2.

Diagnosis of Cancer

Current breast imaging techniques for screening and diagnostic imaging include mammography, breast ultrasound, and breast magnetic resonance imaging (MRI) (*54-57*). Less widely utilized techniques, such as contrast-enhanced mammography, molecular breast imaging, and positron emission mammography, are in use at some institutions or under investigation (*54*). Diagnosis is then made following tissue sampling, such as with biopsy or surgical resection (*54*). Given the invasive nature of biopsy and the technical challenges based on the location of the

lesion (*58*), some clinicians may have an interest in the role of ^{18}F-FES PET in primary breast cancer diagnosis.

Clinical Scenario 1: Diagnosing primary breast cancer (Score: 2 – Rarely Appropriate)

There is currently no literature supporting the use of ^{18}F-FES PET for diagnosing primary breast cancer. Given that ^{18}F-FES PET detects only ER-positive disease (*18*), the 20%–30% of primary breast lesions that are ER-negative (*3-5*) will be missed. Furthermore, small lesions may be below the threshold for PET detection, yet are still clinically important (*59*). Thus, the workgroup recommended that ^{18}F-FES PET is not appropriate for diagnosing primary breast malignancy when biopsy or tissue sampling is available. There may be rare settings in which ^{18}F-FES PET may be considered, such as when mammography, ultrasound, and/or MRI are strongly suggestive of breast malignancy, a biopsy is inconclusive or discordant, and surgical resection is not possible. However, evidence for this clinical scenario is incomplete.

Clinical Scenario 2: Diagnosing malignancy of unknown primary when a biopsy is not feasible or is nondiagnostic (Score: 5 – May be Appropriate)

The workgroup suggested that, in contrast to the first clinical scenario, there may be appropriate applications of ^{18}F-FES PET in the clinical scenario of a lesion or lesions suspicious for ER-positive breast cancer, when the primary malignancy is unknown, and when a biopsy is either not feasible or nondiagnostic. This may be particularly pertinent for a patient with a history of ER-positive breast cancer and a current unknown malignancy. Although the FDA prescribing information (*37*) states not to use ^{18}F-FES PET instead of a biopsy when a biopsy is indicated, ^{18}F-FES PET may be appropriate if a biopsy is not feasible, or if a biopsy has been

performed and the results are not diagnostic. In this scenario, ^{18}F-FES PET may help distinguish an ER-positive breast cancer from an ER-negative malignancy in a patient in which more than one type of malignancy is known or may be present (*10,32,60*).

Initial Staging

Breast cancer is most commonly staged by using the 8th edition of the American Joint Committee on Cancer staging system, which uses primary tumor size (T), nodal involvement (N), and presence of metastases (M), integrated with tumor grade and molecular markers such as ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status, to estimate prognosis (*61*). Imaging is commonly used to assist in the elucidation of TNM staging. T staging is commonly evaluated with mammography, ultrasound, and breast MRI. N staging of breast cancer may be subdivided to evaluate axillary nodes and extra-axillary nodes (*59*). The mainstay of axillary nodal staging is axillary ultrasound and nodal tissue sampling (*62*). Involvement of extra-axillary nodes, such as internal mammary and supraclavicular nodes, is more often based on imaging such as CT and ^{18}F-FDG PET (*63*). M staging may be performed with CT, body MRI, bone scan, and ^{18}F-FDG PET/CT (*64*).

Clinical Scenario 3: Routine staging of the primary tumor (T staging) (Score: 1 – Rarely Appropriate)

T staging of breast cancer relies on tumor size (*61*). Current National Comprehensive Cancer Network (NCCN) guidelines for T staging of primary breast cancer recommend mammography, ultrasound, and/or breast MRI (*64*). Whole-body ^{18}F-FDG PET and ^{18}F-FES PET have lower sensitivity than these methods have (*65*), and windowing of PET examinations

and partial volume averaging effects may alter the apparent size of lesions. Thus, the workgroup believes that standard whole-body ^{18}F-FES PET is rarely appropriate for T staging. Nuclear medicine evaluation of primary breast lesions has been improved by the development of dedicated breast PET and single-photon gamma imaging systems (*66*); however, data that uses ^{18}F-FES on these systems are very limited (*67*).

Clinical Scenario 4: Routine staging of axillary nodes (Score: 3 – Rarely Appropriate)

Clinical classification of regional nodal (N) staging relies on the location of nodal metastases, for example, level I-III axillary, internal mammary, and supraclavicular nodal stations, as well as whether palpable nodes are movable or fixed (*61*). Pathologic classification of regional nodal (N) staging relies on the location, number, and size of nodes (*61*). Level I and II axillary nodes regularly undergo tissue sampling with pathologic diagnosis via percutaneous or sentinel lymph node biopsy or via axillary dissection, whereas the status of level II axillary and extra-axillary nodes is often determined by imaging findings.

There is evidence that ^{18}F-FES PET may detect axillary nodal metastases, even if sub-centimeter (*13,68-70*). The detection threshold depends on relative ER density. Whole-body PET imaging is very unlikely to be more sensitive than pathologic evaluation of sampled axillary nodes, which is available for most patients, provides sensitivity to the level of micrometastases with less than 200 cells, and is the modern standard for axillary nodal staging (*61*). Thus, the workgroup concluded that it would rarely be appropriate to use ^{18}F-FES PET in lieu of tissue sampling for staging of axillary nodes.

Clinical Scenario 5: Routine staging of extra-axillary nodes and distant metastases (Score: 5 – May be Appropriate)

NCCN guidelines for staging of extra-axillary nodal and distant metastases at the time of breast cancer diagnosis include CT and bone scan, with ^{18}F-FDG PET as an optional standard of care (*64*). It is known that ^{18}F-FDG PET may alter breast cancer staging by detection of previously undetected extra-axillary nodal and distant metastases at the time of initial diagnosis (*71-75*), which alters staging, prognosis, and treatment. Far less data are supportive of ^{18}F-FES PET for this clinical scenario. One retrospective study of 19 patients with newly diagnosed breast cancer suggested similar sensitivity of ^{18}F-FES PET to that of ^{18}F-FDG PET, and the addition of ^{18}F-FES PET imaging resulted in a change in management in 26% of patients (*76*). Abstracts have been presented with prospective evidence. However, without published peer-reviewed prospective trials, the workgroup decided further data are needed before making stronger recommendations for ^{18}F-FES PET in this clinical scenario. Prospective trials are needed.

Clinical Scenario 6: Staging invasive lobular carcinoma and low-grade invasive ductal carcinoma (Score: 5 – May be Appropriate)

The term "breast cancer" comprises a wide range of biologically different lesions, characterized by histology and tumor grade, as classified by the World Health Organization (*77*). The most common histology of breast cancer is invasive ductal carcinoma (IDC) of no special type, which accounts for 70%–80% of primary breast malignancies (*78*). The second most common histology is invasive lobular carcinoma (ILC), which accounts for 10%–15% of primary breast malignancies (*78*). ILC is a distinct disease from the more common IDC, with

unique genetic, molecular, and pathologic features (*79*). Breast cancer tumor grade is based on how the cancer cell compares to normal breast epithelial cells, with low-grade implying that a tumor is more similar to normal cells and high-grade implying that a tumor is more unlike normal cells. The terms well differentiated, moderately differentiated, and poorly differentiated are also used to depict tumor grade. Interpretation of breast cancer imaging is influenced by tumor histology and grade. For example, primary ILC is more difficult to detect than IDC on mammography, ultrasound, MRI, and ^{18}F-FDG PET (*80,81*). Regarding metastatic disease, low-grade IDC and ILC malignancies are more likely to display sclerotic osseous metastases and metastases with lower ^{18}F-FDG avidity (*81-83*). ^{18}F-FDG PET/CT has lower rates of detecting distant metastases in ILC than in IDC (*84*). As low-grade IDC and ILC are nearly always ER-positive (*79,85*), investigators have suggested ER-targeted imaging may be of value for patients with these malignancies, particularly when disease is not appreciable on ^{18}F-FDG PET. A head-to-head comparison of patients with metastatic ILC lesions found more than twice as many ^{18}F-FES-avid lesions than ^{18}F-FDG-avid lesions in patients who received both scans within a 5-week period and with no intervening change in disease management (*70*). Nevertheless, the workgroup suggested that larger trials are needed before making stronger recommendations for ^{18}F-FES PET in this clinical scenario. This is another area in which prospective trials and data collection would be valuable.

Biopsy

There are clinical scenarios in which ^{18}F-FES PET may influence the use of biopsy or tissue sampling. In addition to assisting the characterization of a tumor from an unknown

primary (discussed earlier), ^{18}F-FES PET may be used to assess ER status in a lesion or lesions in lieu of biopsy. The workgroup had initially considered an additional clinical scenario in which ^{18}F-FES might be used to direct a biopsy on the basis of the US FDA label stating that ^{18}F-FES is indicated "as an adjunct to biopsy in patients with recurrent or metastatic breast cancer." Further discussion indicated that there were no data to support this scenario yet; therefore, the workgroup decided to omit this clinical scenario from this edition of the AUC, noting that this could be a topic for which future study might be helpful.

Clinical Scenario 7: Assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy (Score: 5 – May be Appropriate)

There were differences of opinion in the workgroup regarding the use of ^{18}F-FES PET in lieu of biopsy to assess ER status when lesions were easily accessible for biopsy. The widely accepted gold standard for determining ER status is biopsy and pathologic evaluation with IHC (*11*). FDA prescribing information states not to use ^{18}F-FES PET in lieu of biopsy when biopsy is indicated (*37*). However, several members of the workgroup noted the high correlation of ^{18}F-FES PET with ER IHC (*9,10,19,32*). Thus, there is reason to favor ER analysis of some lesions by ^{18}F-FES PET. Advantages and disadvantages of using ^{18}F-FES PET in this clinical scenario will need further evaluation. In addition, biopsy of the metastasis is indicated to determine other molecular targets beyond ER, including HER2, PR, and phosphoinositide 3-kinase (*86*). Therefore, the workgroup adopted a neutral position, stating that this is a clinical scenario in which ^{18}F-FES PET may be appropriate.

Clinical Scenario 8: Assessing ER status in lesions that are difficult to biopsy, or when biopsy is nondiagnostic (Score: 8 – Appropriate)

In contrast to their conclusions for the previous clinical scenario, the workgroup regarded the use of ^{18}F-FES PET as appropriate to assess ER status when the lesion(s) are difficult or dangerous to biopsy. There are published examples on the use of ^{18}F-FES PET for this clinical indication (*10*). Indeed, although the FDA prescribing information (*37*) establishes ^{18}F-FES as an adjunct to biopsy, biopsy is not always indicated or desirable. Lesions may be in locations that make biopsy difficult or impose substantial risk. Examples include brain lesions, spinal lesions deep to the spinal cord, or lesions adjacent to major vascular structures. In these cases, the high correlation of ^{18}F-FES PET with ER IHC (*9,10,19,32*) may favor noninvasive imaging over the risks of biopsy. The workgroup believes that ^{18}F-FES PET can provide clinically valuable information when biopsy is difficult or dangerous, or in cases when biopsy was performed but is nondiagnostic.

Selection of Therapy

There is a growing role for targeted imaging to help guide the optimal use of targeted therapies. Somatostatin receptor (SSTR)-targeted PET imaging is used to help select appropriate patients for SSTR-targeted radioligand therapy with ^{177}Lutetium (^{177}Lu)-Dotatate (*87*). Similarly, prostate-specific membrane antigen (PSMA)-targeted PET imaging is used to help select appropriate patients for PSMA-targeted radioligand therapy with ^{177}Lu-PSMA-617 (*88,89*). Although no radioligand therapy currently exists that targets ER, there are numerous non-radioactive endocrine axis therapies. These effective therapies for patients with ER-positive

breast cancer act by decreasing available estrogens, degrading ER, blocking estrogen binding to ER, or decreasing downstream effects of ER signaling (*90*).

As previously stated, the ER status of breast cancer is commonly determined by IHC (*11*). However, the presence of ER by IHC may not be the optimal predictive biomarker for success of endocrine axis therapies. Although most patients with ER-positive breast cancers respond to first-line endocrine axis therapies, fewer respond to second-line or third-line endocrine axis therapies (*91*), and patients with recurrent or metastatic ER-positive breast cancer may develop endocrine resistance, despite remaining ER-positive on IHC (*92*). One reason for this might be disease heterogeneity and sampling error in the one or few biopsied sites. A limited number of biopsies can yield incomplete knowledge about the extent of ER-positive disease in an individual (*12-14,16,17*). Several investigators have studied ^{18}F-FES PET as an alternative and potentially superior predictive biomarker for determining whether patients with breast cancer will be successfully treated by endocrine axis therapies. To date, at least 17 prospective trials have demonstrated ^{18}F-FES PET to be successful in this role (*27-29,33,34,91,93-103*); reviewed in (*60*). These trials represent 547 subjects with ER-positive breast cancer undergoing endocrine axis therapies ranging from the earlier agents such as tamoxifen to the more recent introduction of aromatase inhibitors (AIs) and CDK4/6 inhibitors. There is heterogeneity in these studies with respect to the definition of ER-positivity in the tissue samples, the cutoff for positivity by ^{18}F-FES PET, the definition of response, and the endocrine axis therapies administered; however, the workgroup stated that this body of evidence provided strong support for the use of ^{18}F-FES PET to assist with treatment selection for patients considering endocrine axis therapies. The workgroup then divided this application of ^{18}F-FES PET into where the patient was in the course of their disease, namely, at initial diagnosis of primary breast cancer, at initial diagnosis of

metastatic disease, and when considering additional lines of therapy following progression of metastatic disease.

Clinical Scenario 9: After progression of metastatic disease, for considering second line of endocrine therapy (Score: 8 – Appropriate)

Over 25 years of collective evidence has demonstrated the value of ^{18}F-FES PET in the clinical scenario of predicting response to second- or subsequent-line endocrine therapy following progression on first-line endocrine therapy (*27-29,34,91,93,95,96,98,101-103*). The first published report on this topic, by Mortimer et al. in 1996 (*93*), identified a subset of patients who were ER-positive by in vitro assay but ^{18}F-FES-negative with a SUVmax cutoff of 1. The authors hypothesized that assessment of ER with ^{18}F-FES PET could identify patients whose disease would be refractory to endocrine therapy despite apparent ER-positivity on tissue immunoassay such as IHC. This report was followed by trials demonstrating that ^{18}F-FES PET could distinguish patients who would not respond to endocrine therapies by using SUV cutoffs ranging from 1 to 2 (*94,95*). It was then demonstrated in patients with biopsy-proven advanced ER-positive breast cancer that a pretreatment lesional ^{18}F-FES SUVmax of less than 1.5 was highly predictive of unsuccessful tamoxifen therapy (*95*). Thus, ^{18}F-FES PET could predict which patients should forgo endocrine therapy and could make this prediction better than ER status on IHC could. This remarkable result has been reproducible as newer endocrine axis therapies have been introduced to the care of patients with breast cancer, including fulvestrant, AIs, and synergistic endocrine therapy with CDK4/6 inhibitors. Boers et al. (*101*) evaluated 27 patients with metastatic breast cancer who were ER-positive by IHC and scheduled to receive a modern combination of AI and CDK4/6 inhibitor therapy with letrozole and palbociclib. All

patients underwent ^{18}F-FES PET/CT prior to initiation of therapy. If all known sites of disease were ^{18}F-FES avid, median time to progression was 73 weeks, whereas if all known sites of disease were ^{18}F-FES negative, median time to progression was only 15 weeks. Thus, ^{18}F-FES PET/CT was more valuable in selecting patients for letrozole/palbociclib therapy than was ER IHC alone. This superior predictive effect reflects that ^{18}F-FES samples the body burden of disease, rather than one lesion, and confirms or refutes whether that one lesion is reflective of multiple metastatic sites. Overall, the body of work demonstrates that ^{18}F-FES PET can identify patients with metastatic ER-positive breast cancer who will not respond to endocrine therapy, despite having past and/or present ER-positive characterization by IHC. The workgroup believes that using ^{18}F-FES PET to help define patients with metastatic ER-positive breast cancer who are unlikely to respond to second- or subsequent-line endocrine therapy is appropriate. Given that over 100,000 patients live with ER-positive metastatic breast cancer (*104*), the use of ^{18}F-FES PET for this clinical scenario has the potential to prevent large numbers of patients from receiving ineffective courses of endocrine therapies, saving time, as well as unnecessary side effects and the costs of ineffective treatments.

Clinical Scenario 10: At initial diagnosis of metastatic disease, for considering endocrine therapy (Score: 8 – Appropriate)

Although there is less evidence specifically addressing the use of ^{18}F-FES PET to assist in selecting patients for endocrine therapy at initial diagnosis of metastatic disease (*27-29,91,93-95,97*), the workgroup had consensus that this was another appropriate clinical scenario. Most studies that evaluated patients undergoing first-line endocrine therapy also included patients undergoing second-line endocrine therapy, with one published trial specifying patients for first-

line therapy (*97*). Ongoing clinical trials are using ^{18}F-FES PET specifically for prediction of first-line endocrine therapy (NCT04125277, NCT01957332, NCT02398773). The results of some of these trials are expected in the near future and could influence updates of these AUC.

Clinical Scenario 11: At initial diagnosis of primary breast cancer, for considering endocrine therapy (Score: 1 – Rarely Appropriate)

The workgroup had less support for using ^{18}F-FES PET to determine which patients should receive endocrine therapy at initial diagnosis of a primary breast malignancy. Two trials encompassing 50 patients have specifically addressed this clinical indication (*99,100*). A trial by Park et al. (*99*) evaluated combined endocrine and HER2-targeted therapy in patients with newly diagnosed ER-positive and HER2-positive breast cancer; thus, the relative efficacy of targeting each receptor is unclear. A trial by Chae et al. (*100*) was a substudy of the randomized neoadjuvant study of chemotherapy versus endocrine therapy in postmenopausal patients with primary breast cancer (NEOCENT) trial; the 2 patients with newly diagnosed breast cancer who were ER-positive by IHC but qualitatively negative by ^{18}F-FES were both assigned to the chemotherapy arm, and were the only 2 of 26 patients (13 chemotherapy, 13 endocrine therapy) to have no residual disease at surgery. However, given the small number of patients evaluated in these publications, the fact that neoadjuvant endocrine therapy remains a rapidly progressing field with unresolved issues, and that for other radiotracers, such as ^{18}F-FDG, whole-body PET has better accuracy for distant lesions than for primary breast lesions, the workgroup felt that this is an area requiring further investigation prior to assigning a higher score.

Other Clinical Scenarios

Clinical Scenario 12: Measuring response to therapy (Score: 1 – Rarely Appropriate)

Measuring response to therapy is an area of clear difference between indications for ^{18}F-FES PET and ^{18}F-FDG as radiotracers. Clinicians in the United States have become accustomed to using ^{18}F-FDG PET to monitor response in patients with metastatic breast cancer following administration of therapy, as described in NCCN guidelines (*64*).

Although response criteria in solid tumors (RECIST) are the standard for measuring response to chemotherapy and targeted therapies (*105*), patients with metastatic breast cancer often have bone-dominant disease, which is not measurable by RECIST. PET response criteria in solid tumors (PERCIST) have been developed to monitor therapy response with ^{18}F-FDG PET (*106*), and, in cases of bone-dominant disease, PERCIST can better evaluate response to therapy in patients with metastatic breast cancer than anatomic criteria can in RECIST (*107,108*). Thus, there is likely to be interest in using other PET radiotracers, such as ^{18}F-FES, for evaluation of therapy response in patients with breast cancer. Although serial ^{18}F-FES PET measures ER blockade by blocking agents (*33*) and has been helpful in dose development of therapies such as oral selective estrogen receptor degraders (SERDs) (*35*), the workgroup could find little data supporting the use of ^{18}F-FES PET to measure clinical response. A few published trials obtained multiple ^{18}F-FES PET scans to allow evaluation of changes during treatment. Peterson et al. (*102*) reported no change in ^{18}F-FES avidity following treatment with vorinostat, a histone deacetylase inhibitor hypothesized to restore endocrine sensitivity. Gong et al. (*109*) published results of 22 patients undergoing ^{18}F-FES and ^{18}F-FDG before and after 2 cycles of treatment with docetaxel or docetaxel/fulvestrant. In patients receiving fulvestrant, larger decreases in ^{18}F-

FES SUV were associated with increased progression-free survival. However, successful ER blockade is not a guarantee of clinical benefit, and thus it may be difficult to distinguish changes in numbers of cancer cells from changes in ER expression in those cells. In the worst-case scenario, decreases on ^{18}F-FES PET could be interpreted as response to therapy, when actually a non-ER-expressing clone becomes dominant and grows undetected by ^{18}F-FES PET (*15*). Given this limitation of ^{18}F-FES PET and the lack of data available for evaluating response to therapy with this agent, the workgroup does not believe that ^{18}F-FES PET is currently appropriate for measuring response to therapy. Prospective studies would be needed before making a recommendation supporting this clinical scenario.

Clinical Scenario 13: Detecting lesions in patients with suspected/known recurrent or metastatic breast cancer (Score: 5 – May be Appropriate)

As with the previous clinical scenario, clinicians have also become accustomed to using ^{18}F-FDG PET to evaluate patients with suspected/known recurrent or metastatic breast cancer, as described in NCCN guidelines (*64*). Unfortunately, little evidence is available that has evaluated ^{18}F-FES PET for this clinical scenario. Chae et al. (*69*) published a retrospective review of 46 patients who underwent both ^{18}F-FDG and ^{18}F-FES PET imaging for suspected breast cancer recurrence. ^{18}F-FES PET detected 32 of 45 (71%) recurrences (32 of 41 ER-positive recurrences), and ^{18}F-FDG PET detected 36 of 45 (80%) recurrences, as well as a false-positive benign finding (chronic granulomatous inflammation). A prospective trial of this clinical indication is ongoing (NCT04883814), evaluating ^{18}F-FES PET to standard-of-care imaging (CT/bone scan or FDG PET/CT) for identifying sites of recurrence with pathology as the

reference standard. The workgroup felt that this was an application of some potential, but without further published evidence, a higher score is not currently warranted.

Clinical Scenario 14: Detecting ER status when other imaging tests are equivocal or suspicious (Score: 8 – Appropriate)

It is not uncommon for imaging studies to be inconclusive or equivocal. Lesions on anatomic imaging such as CT or MRI may have imaging features that are not definitively benign or malignant. Imaging with bone scan may be particularly difficult, given the high sensitivity of a bone scan for osseous lesions but more limited specificity for what these lesions represent (*110,111*).

Several studies have evaluated the ability of ^{18}F-FES PET to solve clinical dilemmas when findings on other imaging modalities were equivocal or inconclusive (*112-115*). These clinical dilemmas included uncertainty about the presence or extent of malignancy, unclear ER status, and unclear origin of a metastasis in a patient with 2 known primary malignancies. These 4 studies include ^{18}F-FES PET scans on 181 patients with breast cancer, with more than half of ^{18}F-FES PET scans leading to alterations in patient treatment based on knowledge gained from the ^{18}F-FES PET. The workgroup was unanimous that ^{18}F-FES PET was appropriate for patients with an ER-positive breast cancer and imaging studies that are equivocal when whole-body assessment of ER status by ^{18}F-FES PET could lead to a change in patient management. This approach is most helpful when the ^{18}F-FES PET result is positive.

QUALIFYING STATEMENTS

Evidence Limitations

Although the literature on ^{18}F-FES PET supports the use of this modality in some clinical scenarios, the workgroup recognizes limitations in the available evidence. Many articles have incomplete pathologic correlations and/or limited patient follow-up; thus, the reference standards for assessing sensitivity, specificity, and accuracy may be suboptimal. Data are still limited for multiple potential clinical scenarios, in particular the use of ^{18}F-FES PET for staging or monitoring treatment response, as well as accuracy according to histologic subtype of breast cancer. Scores of the AUC workgroup may change as further evidence becomes available. Prospective randomized trials that evaluate clinical outcomes following use (or non-use) of ^{18}F-FES PET are needed. Many such trials are currently ongoing or completed and awaiting reporting of results. These include trials of ^{18}F-FES as a predictive biomarker of endocrine therapy response at different time points along the course of disease (NCT04692103, NCT04125277, NCT03442504, NCT00602043, NCT01957332, NCT05068726) and trials of ^{18}F-FES for systemic staging and detection of recurrence in patients with IDC and ILC (NCT04883814, NCT04252859, NCT03726931).

Benefits and Harms of AUC Guidance

Benefits of implementing AUC in clinical practice include supplying health care providers with support for the selection of advanced imaging techniques in appropriate clinical scenarios. AUC offer a mechanism to track comparisons between the AUC and the reimbursement policy of payers (*116,117*). This can lead to a more efficient approval process for advanced diagnostic imaging procedures, saving time and effort for physicians and imaging

facilities. In addition, the authors of these AUC anticipate that this document will alert the medical community to where further research is needed and promote investigation in these areas.

There is concern that AUC for medical imaging examinations have the potential to inadvertently and inappropriately prevent access to the imaging techniques described. If AUC do not include a clinical scenario or do not place a high score on a clinical scenario due to limited evidence, then the advanced imaging technique may be denied reimbursement for that clinical scenario, despite a medical professional's judgement that it may be beneficial in an individual case (*117,118*). It is acknowledged that writing AUC for all potential clinical scenarios and keeping the AUC current are difficulties that have the potential to cause harm.

Implementation of This AUC Guidance

SNMMI has been working with several other medical specialty societies to develop broad-based multidisciplinary clinical guidance documents. This collaboration should foster the acceptance and adoption of this guidance by other specialties.

SNMMI has developed a multipronged approach to disseminate the AUC for ^{18}F-FES PET in patients with ER-positive breast cancer to all relevant stakeholders—referring clinicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will be a mix of outreach and educational activities and will be targeted to each of these audiences. SNMMI will create detailed case studies for its members and for referring physicians and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of ^{18}F-FES PET, as well as some cases in which the results of ^{18}F-FES PET are equivocal. Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on these AUC, factsheets, and other didactic

materials will be made available on the SNMMI webpage dedicated to the ^{18}F-FES PET AUC. Live sessions will be held at the SNMMI annual and midwinter meetings, as well as at the relevant societal meetings of referring physicians, to highlight the importance of these AUC. SNMMI also aims to create a mobile application for the ^{18}F-FES PET AUC for both Apple and Android platforms. Mobile applications are becoming increasingly popular in the health care industry and can be used to distribute updates to all users. In addition to these activities, SNMMI will undertake patient-focused outreach to provide education on how AUC can play an invaluable role in achieving a more accurate diagnosis.

Summary

^{18}F-FES is a radiolabeled form of estrogen that binds to ER. PET imaging with ^{18}F-FES allows noninvasive and whole-body evaluation of ER that is functional for binding. These AUC represent the expert opinions of a workgroup convened by the SNMMI to evaluate clinical scenarios for the use of ^{18}F-FES PET in patients with ER-positive breast cancer, based on a comprehensive review of the published literature. The workgroup concluded that the most appropriate uses of ^{18}F-FES PET are for when clinicians are considering endocrine therapy either after progression on a prior line of endocrine therapy or at initial diagnosis of metastatic disease, for assessing ER status of lesions that are difficult or dangerous to biopsy, and for determining ER status in lesions when other imaging tests have inconclusive results.

Table 1: Dosimetry for ^{18}F-FES (*39*)

Organ	
Liver (mSv/MBq)	0.126
Gallbladder wall (mSv/MBq)	0.102
Bladder wall (mSv/MBq)	0.050
Kidney (mSv/MBq)	0.035
Uterus (mSv/MBq)	0.039

Dose	
Effective dose (mSv/MBq)	0.022
Typical injected activity	
MBq	185
mCi	5
Estimated effective dose per scan (mSv)	4.07

MBq: megabecquerel, mCi: millicurie, mSv: millisievert

Table 2: Clinical Scenarios for Estrogen Receptor (ER)-Targeted PET with ^{18}F-Fluorestradiol (^{18}F-FES)

Scenario number	Description	Appropriateness	Score
Diagnosis			
1	Diagnosing primary breast cancer	Rarely appropriate	2
2	Diagnosing malignancy of unknown primary when a biopsy is not feasible or is nondiagnostic	May be appropriate	5
Staging			
3	Routine staging of the primary tumor (T staging)	Rarely appropriate	1
4	Routine staging of axillary nodes	Rarely appropriate	3
5	Routine staging of extra-axillary nodes and distant metastases	May be appropriate	5
6	Staging invasive lobular carcinoma and low-grade invasive ductal carcinoma	May be appropriate	5
Biopsy			
7	Assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy	May be appropriate	5
8	Assessing ER status in lesions that are difficult to biopsy, or when biopsy is nondiagnostic	Appropriate	8
Selection of therapy			
9	After progression of metastatic disease, for considering second line of endocrine therapy	Appropriate	8

10	At initial diagnosis of metastatic disease, for considering endocrine therapy	Appropriate	8
11	At initial diagnosis of primary breast cancer, for considering endocrine therapy	Rarely appropriate	1
Other			
12	Measuring response to therapy	Rarely appropriate	1
13	Detecting lesions in patients with suspected/known recurrent or metastatic breast cancer	May be appropriate	5
14	Detecting ER status when other imaging tests are equivocal or suspicious	Appropriate	8

ER: estrogen receptor, T = primary tumor

APPENDIX A: Workgroup Members and External Reviewers

Workgroup

The members of the workgroup are as follows:
Amy S. Clark, MD, MSCE, University of Pennsylvania, Philadelphia, PA (SNMMI);
Farrokh Dehdashti, MD, Washington University in St Louis, St Louis, MO (SNMMI);
Elisabeth G.E. de Vries, MD, PhD, University Medical Center, University of Groningen, Groningen, Netherlands (SNMMI);
Amy M. Fowler, MD, PhD, University of Wisconsin, Madison, WI (ACNM, SNMMI);
Brenda F. Kurland, PhD (SNMMI);
Hannah M. Linden, MD, University of Washington, Seattle, WA (SNMMI);
David A. Mankoff, MD, PhD, University of Pennsylvania, Philadelphia, PA (SNMMI);
Dae Hyuk Moon, MD, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea (KSNM);
Joanne Mortimer, MD, City of Hope, Duarte, CA (SNMMI);
Jason Mouabbi, MD, The University of Texas MD Anderson Cancer Center, Houston, TX (LBCA);
Lanell M. Peterson, PhD, University of Washington, Seattle, WA (SNMMI); Gary A. Ulaner, MD, PhD (Chair), Hoag Family Cancer Institute, Newport Beach, CA, and University of Southern California, Los Angeles, CA (SNMMI)

External Reviewers

The external reviewers for this AUC are as follows:
Elizabeth H. Dibble, Brown University, Providence, RI;
Kevin Donohoe, Beth Israel Deaconess Medical Center, Boston, MA;
Courtney Lawhn Heath, University of California, San Francisco, San Francisco, CA

SNMMI

The supporting staff from SNMMI for these AUC are Bonnie Clarke, Senior Director, and Doug Burrichter, Program Manager.

APPENDIX B: Summary of Definitions of Terms and Acronyms

ACNM: American College of Nuclear Medicine
AI: aromatase inhibitor
AUC: appropriate use criteria
CDK4/6: cyclin-dependent kinase 4/6
CT: computed tomography
EANM: European Association of Nuclear Medicine
ER: estrogen receptor
^{18}F-FDG: ^{18}F-fluorodeoxyglucose
^{18}F-FES: 16α-^{18}F-fluoro-17β-fluoroestradiol
HER2: human epidermal growth factor receptor 2
IDC: invasive ductal carcinoma
IHC: immunohistochemistry
ILC: invasive lobular carcinoma
KSNM: Korean Society of Nuclear Medicine
LBCA: Lobular Breast Cancer Society
Lu: Lutetium
MBq: megabecquerel
mCi: millicurie
MRI: magnetic resonance imaging
mSv: millisievert
NCCN: National Comprehensive Cancer Network
NCT: National Clinical Trial
NEOCENT: neoadjuvant study of chemotherapy versus endocrine therapy in postmenopausal patients with primary breast cancer
PERCIST: PET response criteria in solid tumors
PET: positron emission tomography
PICOTS: population, intervention, comparisons, outcomes, timing, and setting
PR: progesterone receptor
PSMA: prostate-specific membrane antigen
RECIST: response criteria in solid tumors
SERD: selective estrogen receptor degrader
SERM: selective estrogen receptor modulator
SNMMI: Society of Nuclear Medicine and Molecular Imaging
SSTR: somatostatin receptor
SUV: standardized uptake value
SUVmax: maximum standardized uptake value
TNM: tumor, node, metastasis
US FDA: United States Food and Drug Administration

APPENDIX C: Disclosures and Conflicts of Interest

Relationships with Industry and Other Entities	
Workgroup member	Reported relationships
Amy S. Clark	• Siemens: Honoraria
Farrokh Dehdashti	• AbbVie Inc.: Research support • Siteman Cancer Center: Research support • Trevarx Biomedical, Inc.: Advisory board • Transcend Molecular Imaging Inc.: Advisory board
Elisabeth G. E. de Vries	• Amgen: Research support • AstraZeneca: Research support • Bayer: Research support • Crescendo Biologics: Advisory board/Consultant • Daiichi Sankyo: Advisory board/Consultant • G1 Therapeutics: Research support • GE Healthcare: Research support • Genentech: Research support • NSABP: Advisory board/Consultant • Regeneron: Research support • Roche: Research support • Servier: Research support • Synthon: Research support
Amy M. Fowler	• GE Healthcare: Advisory board • Elsevier: Book chapter royalty
Brenda F. Kurland	• None
Hannah M. Linden	• None
David A. Mankoff	• Blue Earth Diagnostics: In-kind material transfer • Calithera: In-kind material transfer • GE Healthcare: Advisory board, Consultant, Research Support • ImaginAb: Scientific advisory board • Reflexion: Scientific advisory board • Trevarx: Co-Founder, Ownership, Scientific advisory board
Dae Hyuk Moon	• Asan Foundation: Royalties • GE Healthcare: Research support • Life Molecular Imaging GnbH: Research support
Joanne Mortimer	• None
Jason Mouabbi	• GE Healthcare: Advisory board
Lanell M. Peterson	• None
Gary A. Ulaner	• GE Healthcare: Research support, Speaker • ImaginAb: Advisory Board • Lantheus: Advisory Board, Research support, Speaker • National Institutes of Health: Research support • Nuclidium: Advisory Board, Research support

APPENDIX D: Search Terms for Targeted Literature Search

Searches were conducted on PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, and Emcare (through June 30, 2022). Search strategies are defined below.

PubMed
http://www.ncbi.nlm.nih.gov/pubmed?otool=leiden

(("FES"[tw] OR "fluoroestradiol"[tw] OR "fluoroestradiol*"[tw] OR "fluoro estradiol"[tw] OR "fluoro estradiol*"[tw] OR "18ffluoroestradiol"[tw] OR "ffluoroestradiol"[tw] OR "ffluoroestradiol"[tw] OR "16-fluoroestradiol" [Supplementary Concept] OR "Cerianna"[tw] OR ("fluoro"[tw] AND "estradiol"[tw]) OR "fluoroestra"[tw] OR "fluoroestra*"[tw] OR "nsc 743445"[tw] OR "nsc743445"[tw]) AND

("Positron-Emission Tomography"[Mesh] OR "Positron-Emission Tomography"[tw] OR "Positron-Emission Tomogr*"[tw] OR "PET"[tw]) AND

("Breast Neoplasms"[mesh] OR "Breast Neoplasms"[tw] OR "Breast Neoplasm"[tw] OR "Breast Neoplasia"[tw] OR "Breast Cancers"[tw] OR "Breast Cancer"[tw] OR "Breast Carcinomas"[tw] OR "Breast Carcinoma"[tw] OR "Breast Adenocarcinomas"[tw] OR "Breast Adenocarcinoma"[tw] OR "Breast Tumors"[tw] OR "Breast Tumor"[tw] OR "Breast Tumours"[tw] OR "Breast Tumour"[tw] OR "Breast Malignancy"[tw] OR "Breast Malignancies"[tw] OR (("Breast"[tw] OR "Breasts"[tw] OR "Mammary"[tw] OR "Mammaries"[tw]) AND ("Neoplasms"[tw] OR "Neoplasm"[tw] OR "Neoplasia"[tw] OR "Cancers"[tw] OR "Cancer"[tw] OR "Carcinomas"[tw] OR "Carcinoma"[tw] OR "Adenocarcinomas"[tw] OR "Adenocarcinoma"[tw] OR "Tumors"[tw] OR "Tumor"[tw] OR "Tumours"[tw] OR "Tumour"[tw] OR "Malignancy"[tw] OR "Malignancies"[tw])))

NOT (("Case Reports"[ptyp] OR "case report"[ti]) NOT ("Review"[ptyp] OR "review"[ti] OR "Clinical Study"[ptyp] OR "trial"[ti] OR "RCT"[ti])))

MEDLINE via OVID
http://gateway.ovid.com/ovidweb.cgi?T=JS&MODE=ovid&NEWS=n&PAGE=main&D=medall

(("FES".mp OR "fluoroestradiol".mp OR "fluoroestradiol*".mp OR "fluoro estradiol".mp OR "fluoro estradiol*".mp OR "18ffluoroestradiol".mp OR "ffluoroestradiol".mp OR "ffluoroestradiol".mp OR "16-fluoroestradiol"/ OR "Cerianna".mp OR ("fluoro".mp AND "estradiol".mp) OR "fluoroestra".mp OR "fluoroestra*".mp OR "nsc 743445".mp OR "nsc743445".mp) AND

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(exp "Breast Neoplasms"/ OR "Breast Neoplasms".mp OR "Breast Neoplasm".mp OR "Breast Neoplasia".mp OR "Breast Cancers".mp OR "Breast Cancer".mp OR "Breast Carcinomas".mp OR "Breast Carcinoma".mp OR "Breast Adenocarcinomas".mp OR "Breast Adenocarcinoma".mp OR "Breast Tumors".mp OR "Breast Tumor".mp OR "Breast Tumours".mp OR "Breast Tumour".mp OR "Breast Malignancy".mp OR "Breast Malignancies".mp OR (("Breast".mp OR "Breasts".mp OR "Mammary".mp OR "Mammaries".mp) AND ("Neoplasms".mp OR "Neoplasm".mp OR "Neoplasia".mp OR "Cancers".mp OR "Cancer".mp OR "Carcinomas".mp OR "Carcinoma".mp OR "Adenocarcinomas".mp OR "Adenocarcinoma".mp OR "Tumors".mp OR "Tumor".mp OR "Tumours".mp OR "Tumour".mp OR "Malignancy".mp OR "Malignancies".mp)))

NOT (("Case Reports"/ OR "case report".ti) NOT (exp "Review"/ OR "review".ti OR exp "Clinical Study"/ OR "trial".ti OR "RCT".ti)))

Embase
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=main&MODE=ovid&D=oemezd

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(exp "Positron Emission Tomography"/ OR "Positron-Emission Tomography".mp OR "Positron-Emission Tomogr*".mp OR "PET".mp) AND

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NOT (conference review or conference abstract).pt NOT ("case report"/ OR "case report".ti))

Web of Science
http://isiknowledge.com/wos

(TS=("fluoroestradiol f 18" OR "FES" OR "fluoroestradiol" OR "fluoroestradiol*" OR "fluoro estradiol" OR "fluoro estradiol*" OR "18ffluoroestradiol" OR "ffluoroestradiol" OR

"ffluoroestradiol" OR "16 fluoroestradiol" OR "Cerianna" OR ("fluoro" AND "estradiol") OR "fluoroestra" OR "fluoroestra*" OR "nsc 743445" OR "nsc743445") AND

TS=("Positron Emission Tomography" OR "Positron Emission Tomography" OR "Positron Emission Tomogr*" OR "PET")

AND TS=("Breast Cancer" OR "Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Neoplasia" OR "Breast Cancers" OR "Breast Cancer" OR "Breast Carcinomas" OR "Breast Carcinoma" OR "Breast Adenocarcinomas" OR "Breast Adenocarcinoma" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Tumours" OR "Breast Tumour" OR "Breast Malignancy" OR "Breast Malignancies" OR (("Breast" OR "Breasts" OR "Mammary" OR "Mammaries") AND ("Neoplasms" OR "Neoplasm" OR "Neoplasia" OR "Cancers" OR "Cancer" OR "Carcinomas" OR "Carcinoma" OR "Adenocarcinomas" OR "Adenocarcinoma" OR "Tumors" OR "Tumor" OR "Tumours" OR "Tumour" OR "Malignancy" OR "Malignancies")))

NOT DT=(meeting abstract) NOT TI=("case report"))

Cochrane
https://www.cochranelibrary.com/advanced-search/search-manager

(("fluoroestradiol f 18" OR "FES" OR "fluoroestradiol" OR "fluoroestradiol*" OR "fluoro estradiol" OR "fluoro estradiol*" OR "18ffluoroestradiol" OR "ffluoroestradiol" OR "ffluoroestradiol" OR "16 fluoroestradiol" OR "Cerianna" OR ("fluoro" AND "estradiol") OR "fluoroestra" OR "fluoroestra*" OR "nsc 743445" OR "nsc743445") AND

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("Breast Cancer" OR "Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Neoplasia" OR "Breast Cancers" OR "Breast Cancer" OR "Breast Carcinomas" OR "Breast Carcinoma" OR "Breast Adenocarcinomas" OR "Breast Adenocarcinoma" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Tumours" OR "Breast Tumour" OR "Breast Malignancy" OR "Breast Malignancies" OR (("Breast" OR "Breasts" OR "Mammary" OR "Mammaries") AND ("Neoplasms" OR "Neoplasm" OR "Neoplasia" OR "Cancers" OR "Cancer" OR "Carcinomas" OR "Carcinoma" OR "Adenocarcinomas" OR "Adenocarcinoma" OR "Tumors" OR "Tumor" OR "Tumours" OR "Tumour" OR "Malignancy" OR "Malignancies")))):ti,ab,kw

NOT DT=(meeting abstracts)

Emcare
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=main&D=emcr

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(exp "Positron Emission Tomography"/ OR "Positron-Emission Tomography".mp OR "Positron-Emission Tomogr*".mp OR "PET".mp) AND

(exp *"Breast Cancer"/ OR "Breast Neoplasms".ti,ab OR "Breast Neoplasm".ti,ab OR "Breast Neoplasia".ti,ab OR "Breast Cancers".ti,ab OR "Breast Cancer".ti,ab OR "Breast Carcinomas".ti,ab OR "Breast Carcinoma".ti,ab OR "Breast Adenocarcinomas".ti,ab OR "Breast Adenocarcinoma".ti,ab OR "Breast Tumors".ti,ab OR "Breast Tumor".ti,ab OR "Breast Tumours".ti,ab OR "Breast Tumour".ti,ab OR "Breast Malignancy".ti,ab OR "Breast Malignancies".ti,ab OR (("Breast".ti,ab OR "Breasts".ti,ab OR "Mammary".ti,ab OR "Mammaries".ti,ab) AND ("Neoplasms".ti,ab OR "Neoplasm".ti,ab OR "Neoplasia".ti,ab OR "Cancers".ti,ab OR "Cancer".ti,ab OR "Carcinomas".ti,ab OR "Carcinoma".ti,ab OR "Adenocarcinomas".ti,ab OR "Adenocarcinoma".ti,ab OR "Tumors".ti,ab OR "Tumor".ti,ab OR "Tumours".ti,ab OR "Tumour".ti,ab OR "Malignancy".ti,ab OR "Malignancies".ti,ab)))

NOT ("case report"/ OR "case report".ti))

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