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Role and Utility of FES PET Scan in Combination with ctDNA in Clinical Dilemmas

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Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Learning Objectives of FES-PET

1

Understand FES-PET unique mechanism of action which allows visualization of the presence of estrogen receptor.

2

Identify the limitations of FES-PET to ensure safe and effective use.

3

Learn about the clinical utility of FES-PET and its impact on patient management.

4

Review of cases where ctDNA and PET-FES have proved impactful for patients with ER+ recurrent or metastatic breast cancer.

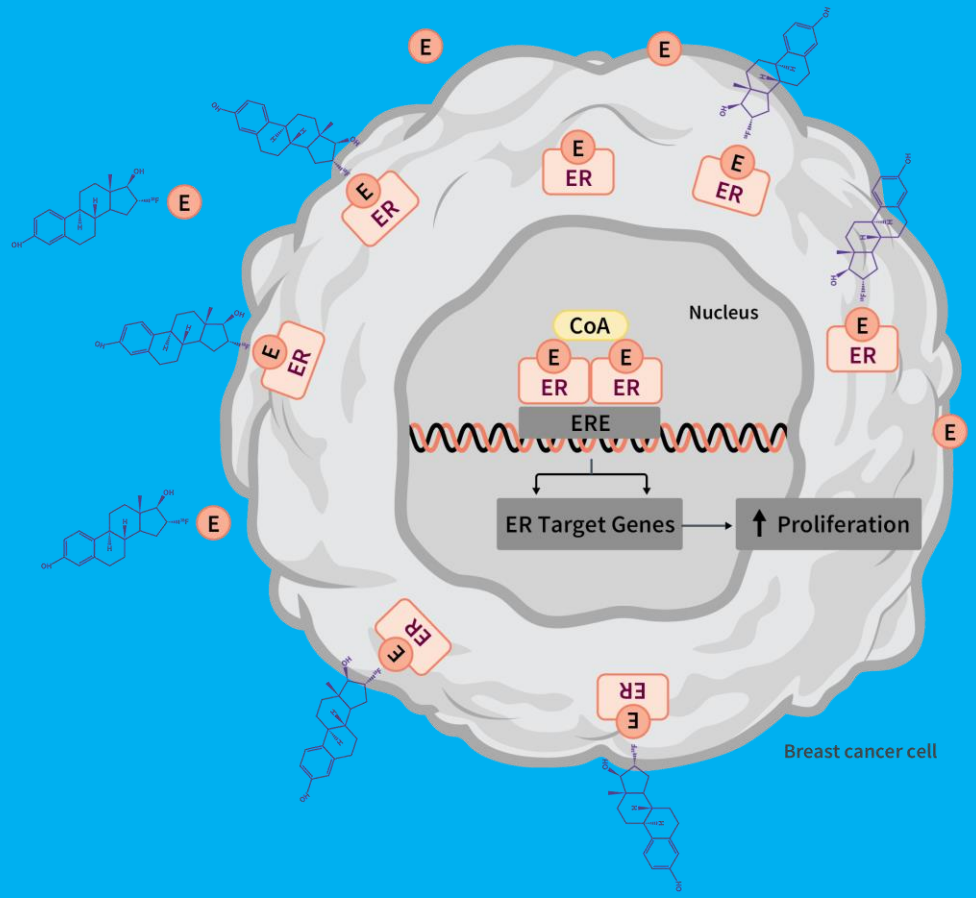
Summary Indications of FES-PET scan

- Evaluating (ER)-positive lesions as an adjunct to biopsy in recurrent or metastatic breast cancer.
- Assessing for metastatic disease and resolve inconclusive findings
- Limitations include confirmation of recurrence of breast cancer and to verify ER status by pathology.
- 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.
- Negative scan does not rule out ER-positive breast cancer.
- Drugs that bind to the ER, including SERMs and SERDs, may compete with the binding of fluoroestradiol F18 and may reduce detection of ER-positive lesions.
- Before administration of FES-PET, discontinue drugs that bind to the ER, such as SERMs and SERDs, for at least 5 biological half-lives: (e.g. elacestrant for 11 days, tamoxifen for 8 weeks and fulvestrant for 28 weeks).

Summary: Appropriate Use Criteria for Estrogen Receptor–Targeted PET Imaging with 16α-^{18}F-Fluoro-17β-Fluoroestradiol. Ulaner et al. JNM. 2023

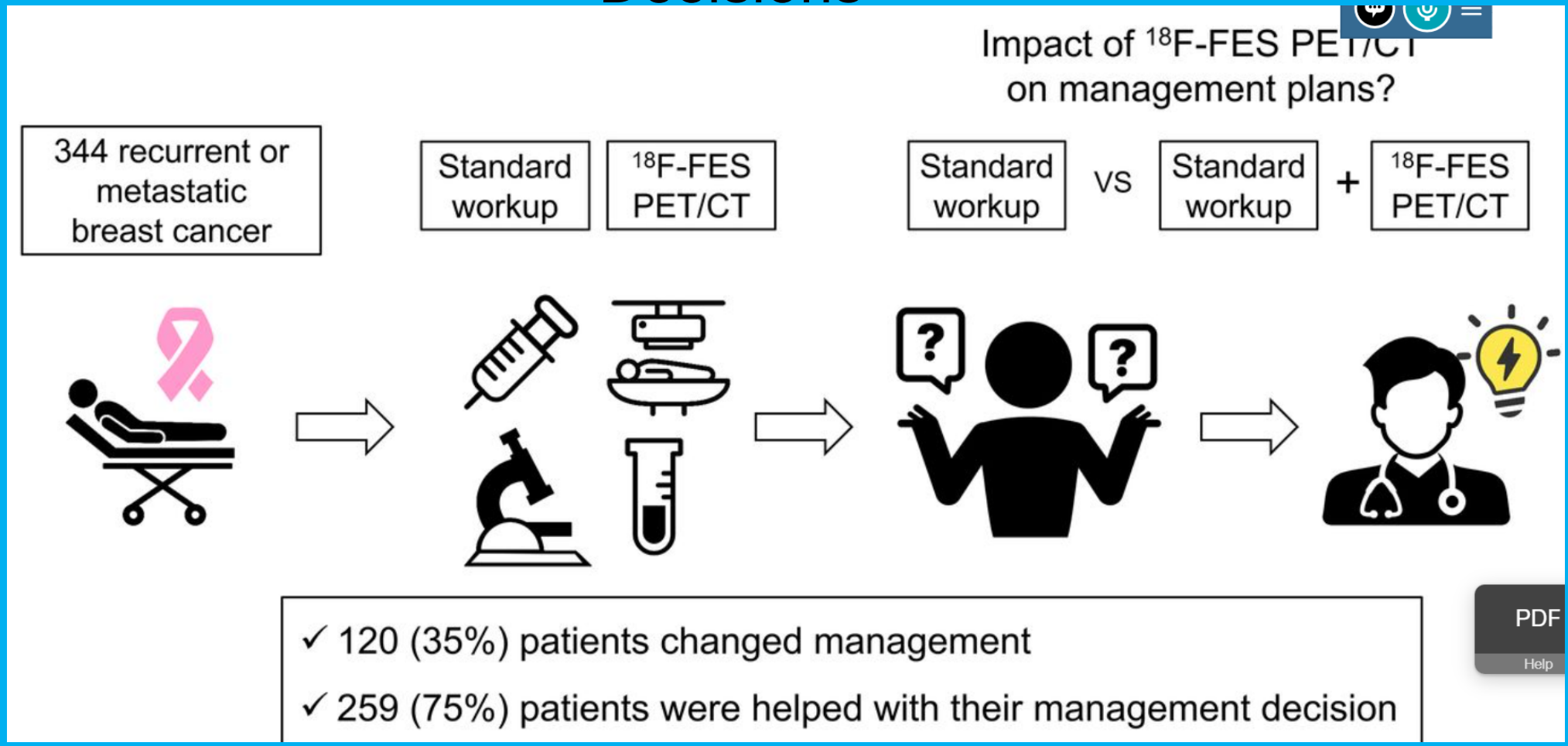
F18 fluoroestradiol (FES) Mechanism of Action

- FES is a radiolabeled estrogen analog that binds to functioning estrogen receptors with relatively high (60-100%) affinity[1,2]
- Utilization of the FES molecule enables PET imaging of lesions with functioning estrogen receptors[1,2]
- FES uptake measured by PET in BC tumors is directly proportional to tumor ER expression measured by in vitro assays[1]
- FES is **NOT** useful for imaging other receptors, such as HER2 and PR, or for assessing regions with high activity due to hepatobiliary and urinary excretion[1,3]



1. Summary: Appropriate Use Criteria for Estrogen Receptor–Targeted PET Imaging with 16α-^{18}F-Fluoro-17β-Fluoroestradiol. Ulaner et al. JNM. 2023
2. van Kruchten M, de Vries EFJ, Glaudemans AWJM, et al. PET imaging of oestrogen receptors in patients with breast cancer. Lancet Oncol. 2013;14(11):e465-e475. doi:10.1016/S1470-2045(13)70374-7.

IMPACT MBC:
FES PET scan Changing the Course of Management and Decisions



Impact of 18F-FES PET/CT on Clinical Decisions in the Management of Recurrent or Metastatic Breast Cancer. Ryu et al. Journal of Nuclear Medicine 2024

IMPACT-MBC Study: Diagnostic Accuracy Analysis[4]

- FES-PET in correlation with standard pathological workup revealed:
  - Sensitivity of 95% or proportion of patients who had an ER-positive tumor on IHC biopsy that the FES-PET successfully flagged.
  - Specificity of 80%
  - Positive predictive value of 93% or patients demonstrating clear positive uptake on an FES scan actually had an ER-positive tumor confirmed on pathology
  - Negative predictive value of 85%.
- High positive predictive value and sensitivity validated FES-PET to act as a highly accurate, non-invasive "virtual biopsy“ and supports the use of FES PET to guide hormonal and endocrine therapy decisions when biopsies are difficult or too risky to undergo.

4. Impact of 18F-FES PET/CT on Clinical Decisions in the Management of Recurrent or Metastatic Breast Cancer. Ryu et al. Journal of Nuclear Medicine 2024

Moving Beyond the Current Standard of Care

	CT scan	FDG PET	FES PET
Mechanism of action	Uses X-rays[5]	Taken up by metabolically active cells[6]	Binds to estrogen receptors (ERs)[7]
What the image shows	Shape and size of tumor[6]	Metabolic activity[6]	ER+ tumor presence and the potential binding ability to estrogen[7]
Relevance to treatment	Evaluates solid tumor treatment response[6]	Provides information about treatment response[6]	May enable tailored treatment planning for breast cancer[7]
Answers	**"Is advanced disease present?"**		**"Is ER+ advanced disease present and is it functioning?"**

- Ryu et al., showed the **addition of FES PET** in managing ER+ recurrent and metastatic breast cancers changes patient management **35%** of the time.[7]
- Cerianna (FES) PET allows for more specific diagnostic insights, redefining and expanding the capabilities of imaging for breast cancer patients.

FES-PET Interactions

- Drugs that bind to the estrogen receptor (ER) may compete with the binding of fluoroestradiol F 18 and may reduce the detection of ER-positive lesions with (FES) PET
- Drugs that bind to the ER, such as SERMs and SERDs, for at least **five biological half-lives**

Approximate duration that therapy may reduce (FES) PET uptake

	Five half-lives
imlunestrant	6.25 days
elacestrant	11 days
tamoxifen	8 weeks
fulvestrant	28 weeks

AIs and CDK 4/6 inhibitors do not need to be withdrawn. These agents deplete estrogen, but do not interfere with the ER or FES PET binding[8,9]

Potential Causes of False Positives

Biological	• Physiological uptake in ER expressing organs such as the uterus and ovaries. • Other tumor types expressing ER (Ovarian, endometrial, meningiomas)
Clinical	• Benign lung atelectasis and radiation pneumonitis
Technical	• Nodal uptake related to Cerianna extravasation

Potential Causes of False Negatives

Biological	• Low ER density/expression • Non-functional ER (ER+ in tissue pathology, but no uptake on Cerianna (FES) PET scan)
Clinical	• Patient scanned while on treatment with SERMs or SERDs, or after insufficient washout
Anatomic location	• Lesions inside or adjacent to organs with high physiological uptake (such as peritoneal and hepatic lesions)
Resolution limitation of PET	• Partial volume effect of PET imaging may cause small lesions (< 1 cm) with moderate uptake to be undetectable over background

Guidelines for Use of FES-PET

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*

FES PET/CT is included as an imaging option for systemic staging of ER+ recurrent/stage IV (M1) disease in the NCCN Guidelines® for Breast Cancer*

Useful in certain circumstances: Consider FES -PET/CT for ER-positive disease and lobular histology*

Not indicated for routine or axillary staging.

Not indicated in early-stage disease and staging the primary.

Not indicated in selecting initial therapy.

Measuring response by therapy.

SNMMI Appropriate Use Criteria (AUC) for 16α-18F-Fluoro-17β-Fluoroestradiol (18F-FES)[15]

Scenario #	Description	Appropriateness
8	Assessing ER status in lesions that are difficult to biopsy, or when biopsy is nondiagnostic	Appropriate
9	After progression of metastatic disease, for considering second line of endocrine therapy	Appropriate
10	At initial diagnosis of metastatic disease, for considering endocrine therapy	Appropriate
14	Detecting ER status when other imaging tests are equivocal or suspicious	Appropriate

Learning Objectives of ctDNA

1

Understand utility of ctDNA monitoring and the assays in practice

2

Identify the limitations of tumor informed and uninformed assays.

3

Learn about the clinical utility of ctDNA assays and its impact on guiding treatment and tracking resistance.

4

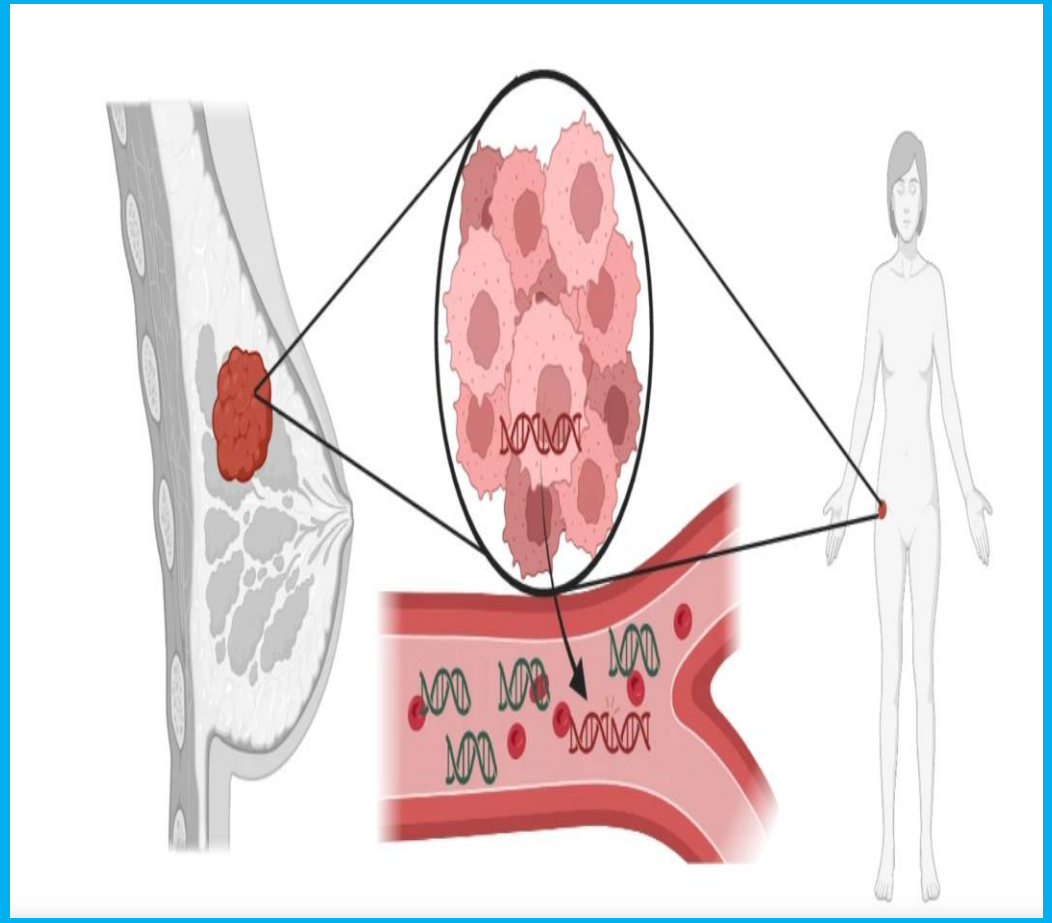
Review of cases where ctDNA and PET-FES have proved impactful for patients with ER+ recurrent or metastatic breast cancer.

Importance of Circulating Tumor DNA in Treatment Decisions In Breast Cancer

- Based on current ASCO guidelines, ctDNA can identify therapy resistant mutations before clinical progression.
- Identification of ESR 1 or PIK3CA or AKT1 allows switching to therapies which can prolong progression free survival.
- In early-stage disease, “lead time to relapse”, ctDNA can predict relapse 8 to 10 months before traditional imaging.
- ASCO surveillance guidelines advised against using it outside of clinical trials in early stages.

The Clinical Utility Dilemma in Early-Stage Care

- “Lead time bias” - finding cancer fragments months before a tumor grows does not alter eventual outcomes.
- “Over treatment risk” proving that adding aggressive therapy or switching drugs with molecular relapse does not essentially impact or save lives.
- Interventional clinical trials underway to evaluate the changing landscape.



ctDNA Based Paradigm Shifting Clinical Trials

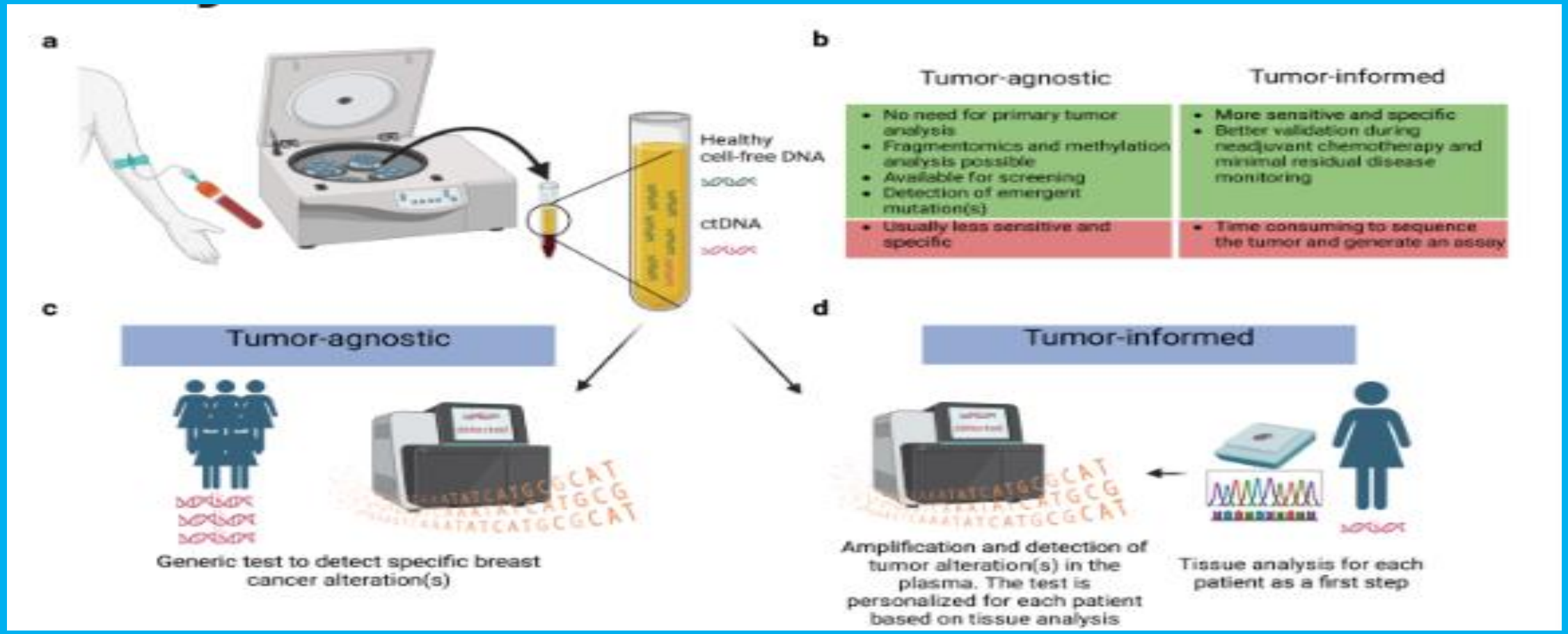
Trial	Phase / Setting	Primary Objective	Treatment Strategy
SERENA-6	**Phase III** Metastatic Setting	**Preempting treatment resistance** by tracking emerging *ESR1* mutations in ctDNA during first-line therapy.	Switching from an aromatase inhibitor (AI) to the novel oral SERD **camizestrant** plus a CDK4/6 inhibitor .[1]
LEADER	**Phase II** Early-stage / Localized setting	**Eliminating molecular residual disease (MRD)** in high-risk patients who after curative treatment with positive ctDNA.	Escalates therapy by adding **ribociclib** in combination with standard adjuvant endocrine therapy. [2]
DARE	**Phase II** Early-stage setting	**Intervening at molecular relapse** in high-risk patients who have completed curative therapy but test positive for ctDNA.	Randomizes patients to current adjuvant hormone therapy or switch to **fulvestrant plus palbociclib**. [3]

1. Bidard FC, Mayer EL, Park YH, et al. First-line camizestrant for emerging ESR1-mutated advanced breast cancer. The New England Journal of Medicine, 2025;393(6):569-580
2. DNA-guided Second Line Adjuvant Therapy for High Residual Risk, Estrogen Receptor Positive, HER-2 Negative Breast Cancer (DARE) (DARE) NCT04567420
3. Sprnt et la. Adjuvant endocrine therapy with cyclin-dependent kinase 4/6 inhibitor, ribociclib, for localized hormone receptor-positive/HER2- breast cancer (LEADER) . NPJ Breast Cancer. . 2025 Jan 7;11(1):2.

Recent FDA Approvals and Possible Historic Shift

- FDA granted accelerated approval to camizestrant based on the dramatic progression-free survival (PFS) extensions demonstrated in the Phase III SERENA-6 trial.
- SERENA-6 nearly doubled median PFS to 16 months.
- SERENA-6 navigates the advanced metastatic field.
- The early-stage DARE trial and LEADER trial continue to offer data regarding whether catching and treating microscopic recurrences in the blood can prevent full metastatic relapse entirely.

What Are the Assays?



Key Features of Tumor-Informed and Uninformed Assays

Features	Tumor-Informed	Tumor-Uninformed
Definition	Patient-specific test	Fixed, standardized test panel
Tissue Requirement	Required	Not required
Personalization	Custom genomic signature unique to the patient's tumor.	Uses a "one-size-fits-all" mutation panel.
Analytical Sensitivity	Excellent for tracking low-level ctDNA in early-stage settings.	May miss rare or non-canonical patient-specific mutations.
Turnaround Time	Requires weeks to sequence tissue	Faster; blood processing can begin immediately.
Clinical Scenarios	Ideal when high sensitivity is needed and archival tissue is available.	Useful when tissue is unavailable, low quality, or results are needed urgently.

Utility of FES-PET For Metastases That Difficult to Biopsy

Patient No.1 – Clinical Vignette

- 69-year-old female with a AJCC Stage IB pT2pN0, grade 2 invasive ductal carcinoma, ER and PR positive in 1999 which was treated with a left breast lumpectomy followed by radiation and tamoxifen-based therapy.
- New right breast mass in October 2023 and underwent biopsy revealing a invasive ductal carcinoma, grade 2, ER positive (90%), PR positive (80%), and HER2/neu 1+. Oncotype 15.
- Right breast lumpectomy followed by adjuvant radiation therapy which was completed 1/25/2023.
- Adjuvant Letrozole in combination with Abemaciclib in February 2023. Her germline testing was negative.

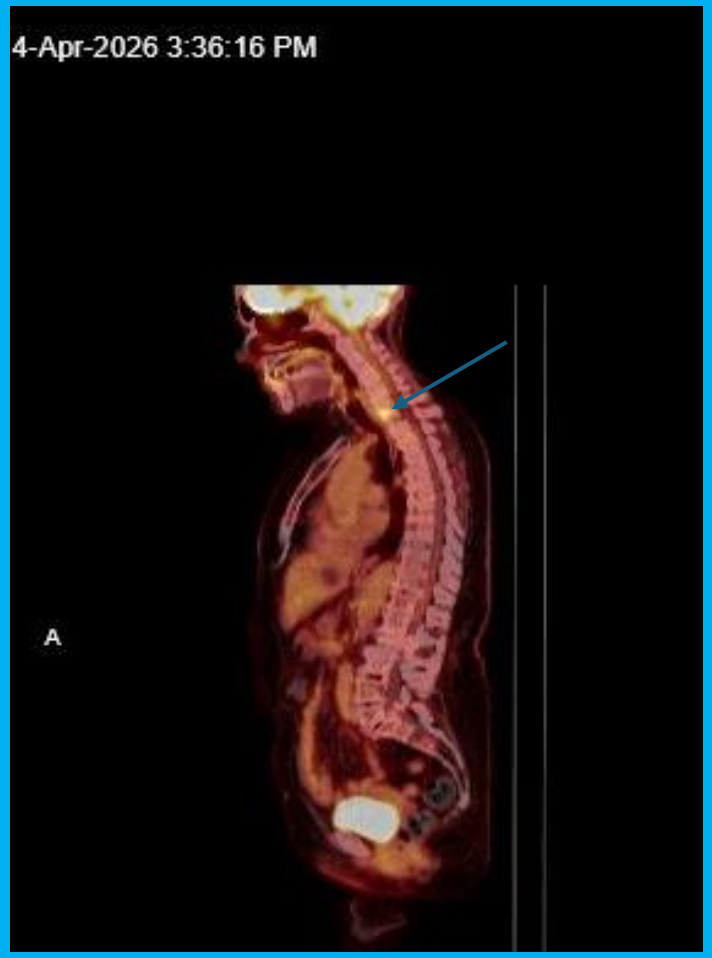
Clinical Vignette - continued for Patient 1

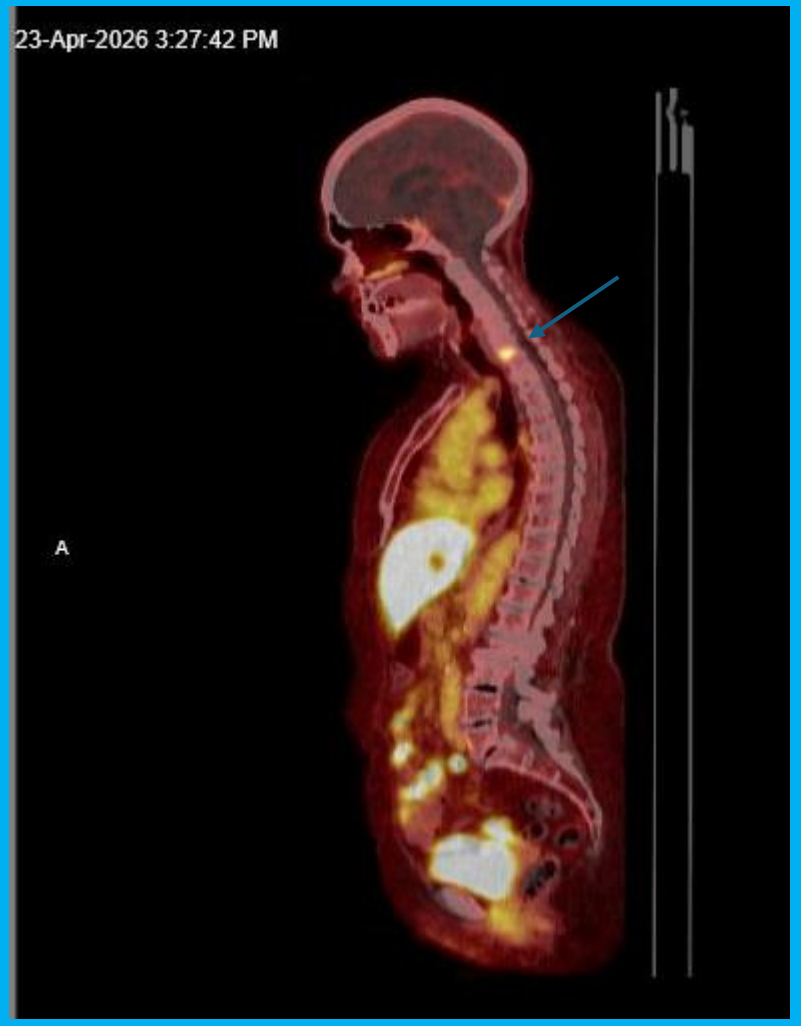
- Completed 2 years of adjuvant endocrine therapy in February 2026.
- March 2026, complained of neck pain with flexion and extension.
- Initial X-rays revealed a subtle lesion a C7.
- Her rheumatologist had ordered an ESR which was slightly elevated at 60 and tumor markers with a CEA which was 6.2 and a normal CA 15.3.

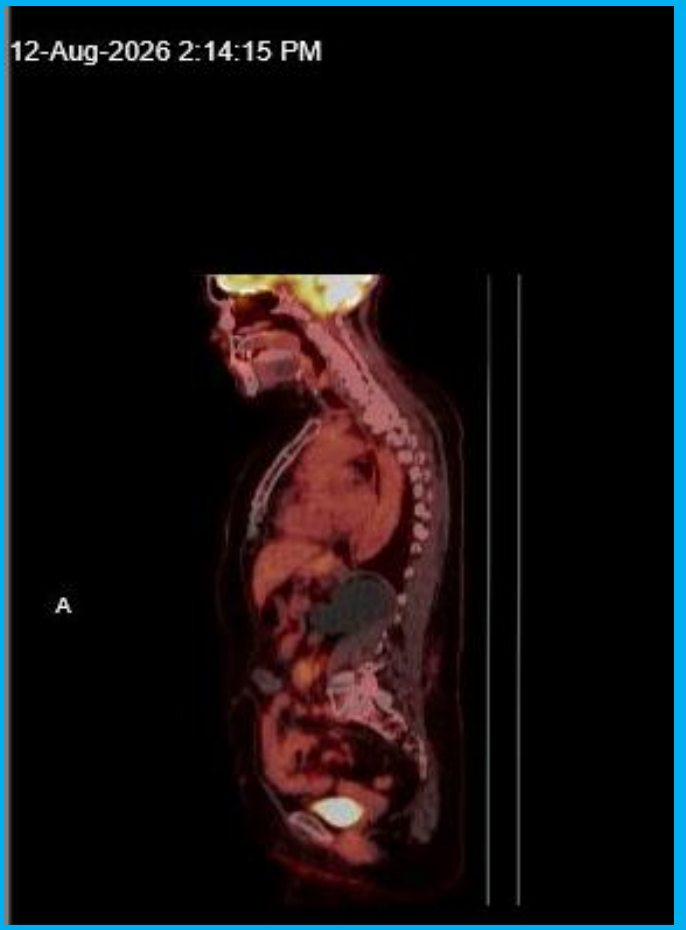
Clinical Vignette - continued for Patient 1

- FDG-PET on 4/14/26 revealed C7 disease.
- Interventional Radiology and Neurosurgery deemed to difficult to perform a biopsy.
- FES-PET on 4/23/26 confirmed the C7 disease seen on initial FDG-PET imaging.
- Initial circulating Tumor DNA was found to be minimal at 0.15.
- Liquid biopsy revealed a non-germline ATM mutation and no evidence of a ESR 1 mutation.

Current and Recent PET imaging







Clinical Vignette - continued for Patient 1

- Started on Faslodex monthly with Ribociclib on 5/15/26.
- Circulating Tumor DNA was found to be minimal at 0.15 on 4/27/26 on Signatera and Guardant 360 testing revealed a non-germline ATM mutation.
- She completed SBRT 30 Gy in 5 fractions to the C7 completed on 5/10/26.
- Reported no pain post-completion of therapy.

Clinical Vignette - continued for Patient 1

- Circulating Tumor DNA was negative as 6/16/26.
- FDG-PET completed on 8/12/26 revealed no evidence of uptake.
- Tolerated the treatment well with mild alopecia, grade 1 leucopenia as well as ongoing muscle and joint pains.

Utility of FES-PET For Lobular Carcinoma

Patient No.2 – Clinical Vignette

- 53-year-old female with AJCC Stage IIIA ypT1c ypN3a cM0, grade 2, ER positive, PR positive, HER2/neu negative, left breast invasive lobular carcinoma 5/15/2016
- Neoadjuvant chemotherapy with dose dense Adriamycin and Cytoxan followed by weekly paclitaxel (6/11-12/20/16)
- Left breast mastectomy with sentinel node evaluation followed by DIEP flap reconstruction January 2017.
- Adjuvant radiation to the left axilla and axillary lymph nodes followed by tamoxifen for 5 years (2017-2022)
- Bilateral risk-sparing oophorectomy in July 2021.

Patient No.2 – Clinical Vignette (continued)

- In May 2025, new onset symptoms of lower back pain.
- Conventional imaging including x-ray and CT did not confirm disease.
- FES PET scan was performed on 8/22/2025 which revealed uptake at T12 with an SUV of 5.6 and L5 with an SUV 6.0.
- Patient underwent a T12 biopsy 8/28/2025 which revealed metastatic lobular carcinoma, ER positive, PR low positive and HER2/neu 1+.

Patient No.2 – Clinical Vignette (continued)

- Patient initiated on anastrozole and palbociclib on 9/11/2025.
- Palliative radiation therapy to L5 completed in September 2025.
- Significant decline in circulating tumor DNA from September to November 2025.
- FES PET completed 6/11/2026 revealed no further uptake at T12 and the L5 vertebral body with an SUV of 3.8.

FES-PET Imaging

Decline in Circulating Tumor DNA Based Upon Diagnosis by FES PET

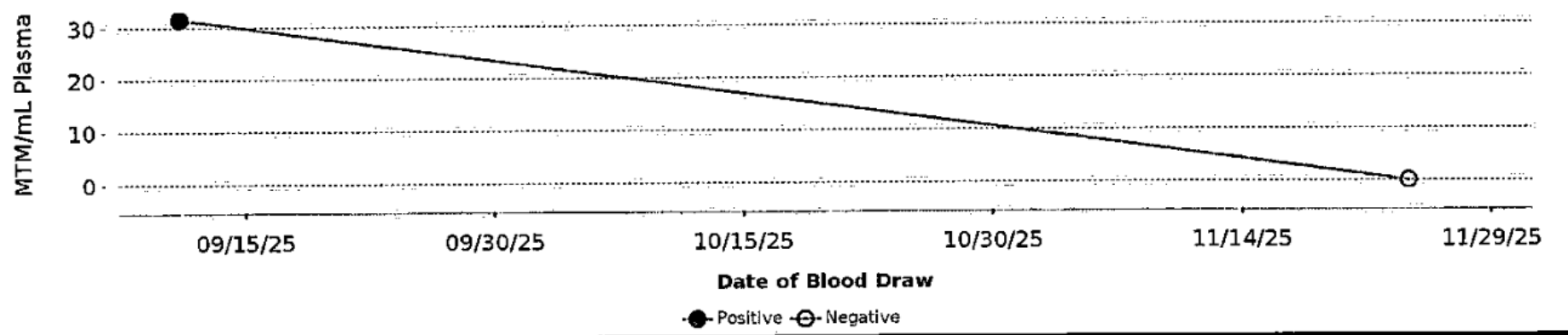
FINAL RESULTS SUMMARY

Signatera Negative

MTM/mL: Not Detected

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. See Limitations section below.

Historical Results



Date	Reported MTM/mL
Nov 24, 2025	0.00
Sep 11, 2025	31.53

Summary of Objectives and Discussion

- FES PET/CT is included as an imaging option for systemic staging of ER+ recurrent/stage IV disease in the NCCN Guidelines® for Breast Cancer.
- Useful in certain circumstances: Consider FES -PET/CT for ER-positive disease and lobular histology*
- Limitations include confirmation of recurrence of breast cancer and to verify ER status by pathology.
- Based on current ASCO guidelines, ctDNA can identify therapy resistant mutations before clinical progression.
- Recent approval of camizestrant based upon early-switching strategy may provide a blueprint for future trials.
- Interventional clinical trials underway to evaluate the changing landscape.

Thank You