Journal of Clinical and Translational Pathology **2026** | Epub
DOI: 10.14218/JCTP.2026.00032

Mini Review

ESR1 Testing in the Era of Precision Oncology: A Mini Review

Liu Liu and Yihong Wang*

Department of Pathology and Laboratory Medicine, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA

Received: June 17, 2026 | **Revised:** August 12, 2026 | **Accepted:** September 08, 2026 | **Published online:** September 16, 2026

Abstract

Background and objectives: Estrogen receptor alpha, encoded by the *ESR1* gene, is a major oncogenic driver in hormone receptor-positive/HER2-negative breast cancers. While endocrine therapies are effective in treating this subgroup, patients with advanced or metastatic disease may develop resistance associated with acquired somatic *ESR1* mutations. This mini review summarizes recent clinical and technological advances in understanding *ESR1* mutations, newly approved targeted therapies, and the use of liquid biopsy companion diagnostics, with a focus on their implications for pathologists.

Methods: We conducted a narrative review of PubMed-indexed literature and relevant regulatory and guideline sources related to *ESR1* in breast cancer, with an emphasis on recent peer-reviewed studies of *ESR1* mutations and clinical trials of emerging therapies.

Results: This review describes the molecular features of *ESR1* alterations and estrogen receptor pathway biology, the mechanisms and key trial data for recently approved ER-targeted therapies for *ESR1*-mutated breast cancer. Additionally, it evaluates liquid biopsy testing platforms for detecting *ESR1* mutations, discusses the advantages and limitations of liquid biopsy in detection of treatment resistance, and considers the evolving role of pathologists in breast cancer care.

Conclusions: Acquired *ESR1* mutations are major drivers of endocrine therapy resistance. Next-generation sequencing and liquid biopsy have increasingly informed the clinical management of breast cancer in the past decade. Pathologists can play an important role in implementing molecular testing, interpreting complex biomolecular data, and helping to guide timely treatment decisions in the era of precision oncology.

Introduction

The normal development and proliferation of breast epithelium are regulated by estrogen, which acts as the primary driver of pubertal growth, and by progesterone, which directs the expansion of the adult mammary epithelium.[1] The historical link between these hormones and malignancy has been recognized for over a century.[2] Jensen's 1967 characterization of the estrogen receptor (ER) protein fundamentally changed the understanding of hormone function and established the ER as a molecular target for endocrine therapy (ET).[3] Approximately 75% of breast cancers are hormone receptor-positive, and those patients benefit from ET, such as the traditional selective estrogen receptor modulator (SERM) tamoxifen and aromatase inhibitors, which effectively block these signaling pathways.[4,5]

With the advent of new-generation SERMs, selective estrogen receptor degraders (SERDs), and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, recent clinical trials such as SERENA-6, VERITAC-2, and CAPItello-291, as well as the ongoing SERENA-4 trial, represent a major shift in the treatment approach for hormone receptor-positive/HER2-negative advanced and metastatic breast cancer. Collectively, these trials reflect a shift toward more personalized, biomarker-driven therapeutic strategies that improve clinical outcomes in defined patient populations.[6-8] *ESR1* mutations are associated with metastatic disease progression and worse clinical outcomes. Real-time testing for *ESR1* mutations using circulating tumor DNA (ctDNA)-based liquid biopsy at disease progression is increasingly used to guide treatment decisions.

Keywords: Breast cancer; *ESR1* mutation; Selective estrogen receptor degrader (SERD); Selective estrogen receptor modulator (SERM); Precision oncology; Liquid biopsy; Molecular pathology.
***Correspondence to:** Yihong Wang, Department of Pathology, Rhode Island Hospital and Brown University Health, Providence, RI 02903 USA. ORCID: https://orcid.org/0000-0003-1252-5579. Tel: +1-401-444-9897, Fax: +1401-444-4377, E-mail: Yihong_wang@brown.edu
How to cite this article: Liu L, Wang Y. *ESR1* Testing in the Era of Precision Oncology: A Mini Review. *J Clin Transl Pathol*. Published online: Sep 16, 2026. DOI: https://doi.org/10.14218/JCTP.2026.00032.

As breast pathology advances and new diagnostic modalities emerge, pathologists are taking on expanded roles. By helping clinicians interpret molecular testing results and identify molecular biomarkers, pathologists are becoming increasingly involved in the era of precision medicine. This mini review highlights recent developments in *ESR1* testing and their clinical implications, with a focus on the practical challenges of implementing and interpreting *ESR1* testing as targeted therapies become more widely integrated into breast cancer care.

ESR1 and the ER signaling pathway

Hormone receptor-positive/HER2-negative breast cancer is the most prevalent molecular subtype of breast cancer. Estrogen receptor alpha (ERα), encoded by the *ESR1* gene, acts as a major oncogenic driver and therapeutic target in approximately 75% of breast cancer cases.[9] Estrogen binding to ER induces receptor dimerization and nuclear translocation, followed by binding to estrogen response elements and transcription of target genes responsible for cell proliferation, survival, and differentiation. ER signaling is not limited to direct DNA binding; it also interacts bidirectionally with kinase pathways, including the PI3K-AKT-mTOR and RAS-RAF-MEK pathways: ER can activate kinase signaling, and kinases can phosphorylate ER to promote ligand-independent transcription (Fig. 1).[10] This cross-talk is a major mechanism of drug resistance in hormone receptor-positive breast cancer.

Next-generation endocrine therapies

Endocrine therapy (ET) has long been used to treat breast cancer. The traditional SERM tamoxifen, approved by the U.S. Food and Drug Administration (FDA) in 1977, competitively binds to estrogen receptors, blocking ER signaling.[11] The first-generation SERD fulvestrant, approved by the FDA in 2002, requires intramuscular injections. Fulvestrant can bind to the ER, induce structural changes that destabilize the protein complex, and trigger ER degradation.[12]

Patients with advanced or metastatic hormone receptor-positive breast cancer can develop endocrine resistance because of acquired somatic *ESR1* mutations; next-generation therapies have been developed to overcome this resistance. Agents in three main therapeutic classes have received FDA approval or fast-track designation in recent years: oral SERDs, SERMs, and proteolysis-targeting chimeras (PROTACs).[13,14] Additional novel drug classes include complete estrogen receptor antagonists. Selective estrogen receptor covalent antagonists are also under active investigation.[13]

SERMs work by competing with endogenous estrogen for binding to the ER, while leaving the receptor intact. SERDs are considered pure antagonists. When a SERD binds to the ER, it induces a receptor conformational change, impairing dimerization and nuclear translocation and promoting degradation through the ubiquitin-proteasome system. PROTACs represent a newer targeted protein-degradation strategy. A PROTAC molecule, functioning as a heterobifunctional protein degrader, is designed to bind to the ER at one end and an E3 ubiquitin ligase at the other. By bringing either wild-type or mutant ER into proximity with the E3 ligase, a PROTAC promotes ER ubiquitination and proteasomal degradation.[15]

The FDA approved the SERD elacestrant (Orserdu, Stemline Therapeutics, Inc.) in 2023 for postmenopausal women or adult men, the SERD imlunestrant (Inluriyo, Eli Lilly and Company) in 2025, and the PROTAC vepdegestrant (Veppanu, Arvinas Operations, Inc.) in 2026 for adults with ER-positive/HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of ET. These approvals were based on the EMERALD (NCT03778931), EMBER-3 (NCT04975308), and VERITAC-2 (NCT05654623), respectively.[6,16-20] The next-generation SERDs, SERMs, and PROTACs that are FDA-approved or under active investigation in late-phase trials are summarized in Table 1. In addition, the SERM lasofoxifene has been granted fast-track designation by the FDA for patients with hormone receptor-positive/HER2-negative metastatic breast cancer with *ESR1* mutations.[21,22] Camizestrant (Etcamah, AstraZeneca) received FDA accelerated approval in September 2026 in combination with a CDK4/6 inhibitor for adults with hormone receptor-positive/HER2-negative locally advanced or metastatic breast cancer upon detection of an *ESR1* mutation during aromatase inhibitor and CDK4/6 inhibitor therapy, based on an FDA-authorized test.[23] Giredestrant remains under phase 3 evaluation.

For elacestrant, imlunestrant, vepdegestrant, and camizestrant, the FDA has approved the Guardant360 CDx liquid biopsy assay as a companion diagnostic to identify patients with *ESR1* mutations for the corresponding treatment indications.[16,17,20,23] This highlights the growing importance of liquid biopsy testing in contemporary breast cancer management.

ctDNA testing for *ESR1* mutation detection

The recent approvals of next-generation endocrine therapies together with the approval of the Guardant360 CDx assay as a companion diagnostic reflect an increasing emphasis on precision medicine in endocrine-resistant breast cancer. Because these therapies are indicated for patients whose tumors harbor *ESR1* mutations, their appropriate use depends on the timely and accurate detection of these actionable *ESR1* mutations.

ESR1 alterations, specifically missense mutations in the ligand-binding domain (LBD) of the ER protein, are recognized as a major acquired resistance mechanism in patients with hormone receptor-positive/HER2-negative metastatic breast cancer receiving ET.[24,25] Residues E380, S463, V534, Y537, and D538 are recurrently altered, with Y537S, Y537N, Y537C, and D538G among the hotspot variants. These *ESR1* LBD mutations stabilize the active conformation of helix 12, allowing transcriptional activity even when estrogen levels are suppressed by aromatase inhibition, and result in constitutive activation of the ER pathway independent of estrogen.[26]

ESR1 mutations are uncommon in untreated primary breast cancer but become substantially enriched in metastatic hormone receptor-positive/HER2-negative disease after ET. *ESR1* mutations are more frequently observed in treated metastatic disease (36%) than in the adjuvant setting (6%) or ET-naïve metastatic breast cancer (< 1%).[27] Testing primary tumor tissue may yield more negative results and may not reflect tumor evolution during treatment. Therefore, testing for *ESR1* mutations in blood samples collected during treatment may provide contemporaneous tumor information to guide treatment decisions.[28] ctDNA-based liquid

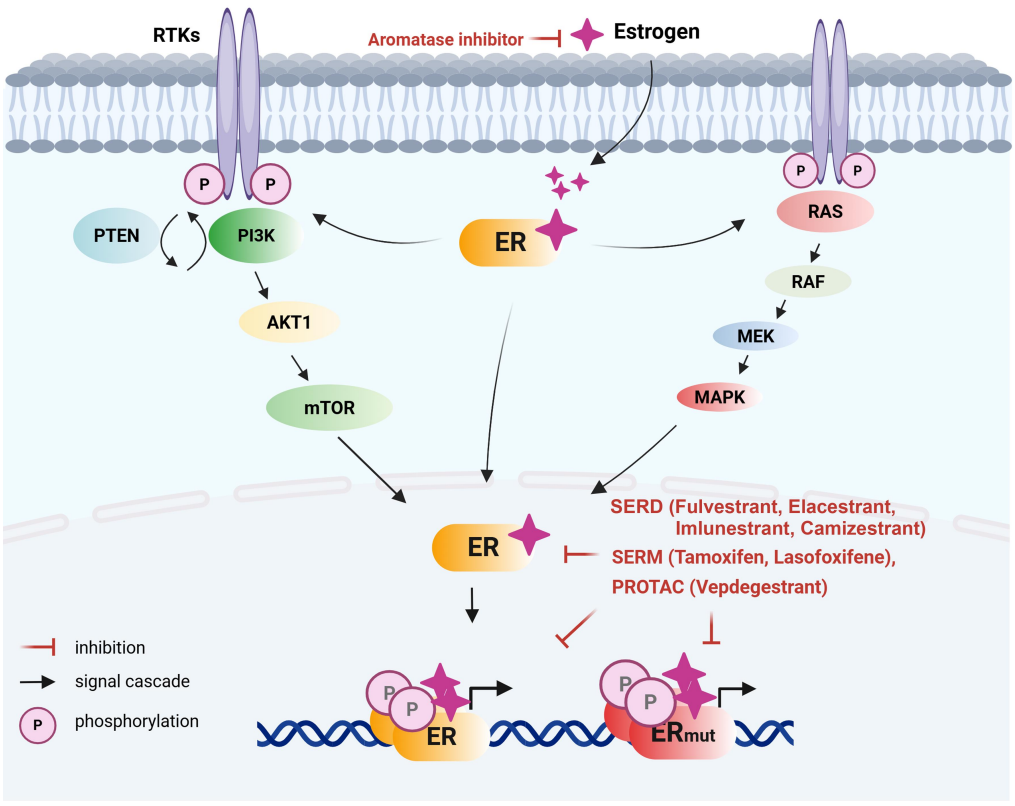

Fig. 1. ER signaling pathways and inhibitors. Estrogen binding induces ER dimerization and activates estrogen response element (ERE)-driven transcription. PI3K and RAS signaling pathways can phosphorylate and activate ER; these pathways can also be activated by ER. Aromatase inhibitors block the enzyme aromatase, which converts androgens into estrogen, thereby lowering estrogen levels. *ESR1* ligand-binding domain (LBD) mutations are associated with endocrine resistance. New-generation drugs include SERDs, SERMs, and PROTACs that can target ER. Created with BioRender.com. AKT1, AKT serine/threonine kinase 1; ER, estrogen receptor; ERmut, mutant estrogen receptor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; P, phosphorylation; PI3K, phosphatidylinositol 3-kinase; PROTAC, proteolysis-targeting chimera; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; RTK, receptor tyrosine kinase; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

Table 1. Next-generation SERDs, SERMs, and PROTACs

Drug name	Drug class	Study	FDA status
Elacestrant	SERD	EMERALD (NCT03778931)	Approved 2023
Imlunestrant	SERD	EMBER-3 (NCT04975308)	Approved 2025
Camizestrant	SERD	SERENA-6 (NCT04964934)	Accelerated approval 2026
Giredestrant	SERD	persevERA (NCT04546009)	Not yet approved
Lasofoxifene	SERM	ELAINE 1 (NCT03781063); ELAINE 2 (NCT04432454)	Fast-track designation
Vepdegestrant	PROTAC	VERITAC-2 (NCT05654623)	Approved 2026

FDA, Food and Drug Administration; PROTAC, proteolysis-targeting chimera; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

biopsy testing can help identify patients who are not responding to treatment or who are at higher risk of relapse. Studies indicate that ctDNA may track treatment response and help predict recurrence in early-stage disease.[29,30] Plasma ctDNA has shown higher detection rates for *ESR1* mutations than tissue testing in some studies.[31]

Liquid biopsy, a minimally invasive method for monitoring tumor recurrence, is increasingly used in clinical oncology. Cell-free DNA extracted from blood and containing tumor-derived ctDNA offers a less invasive option than tissue biopsy. Two major molecular assay designs are used in clinical practice. Targeted

next-generation sequencing (NGS) panels can detect *ESR1* mutations along with alterations in other important genes, such as *PIK3CA*, *AKT1*, *PTEN*, and *ERBB2*, thereby supporting broader therapeutic planning and identifying additional actionable biomarkers. Highly sensitive polymerase chain reaction-based approaches, including droplet digital polymerase chain reaction, can efficiently interrogate known *ESR1* hotspot variants but provide less comprehensive genomic profiling. The clinical utility of liquid biopsy was demonstrated in the PADA-1 trial, where multiplex droplet digital polymerase chain reaction was employed for serial *ESR1* mutation monitoring and a preemptive treatment switch upon detection of an *ESR1* mutation significantly improved progression-free survival.[32] Similarly, in the SERENA-6 trial, switching to camizestrant plus a CDK4/6 inhibitor when an *ESR1* mutation was detected by NGS prolonged progression-free survival.[33] On the basis of findings across multiple studies, guidelines now recommend ctDNA testing for *ESR1* mutations in patients with hormone receptor-positive/HER2-negative metastatic breast cancer.[34,35] As the cost of NGS has decreased in recent years, comprehensive NGS profiling has become a more widely used strategy and can assess an increasing number of biomarkers (Fig. 2).

Nevertheless, although liquid biopsy can support disease monitoring and recurrence detection, it has important technical limitations. It may be less sensitive than tissue-based NGS when a blood sample contains a low tumor fraction, whereas a tissue sample may be more enriched in tumor material. Fluctuations in ctDNA levels may correlate with the course of the disease; a higher tumor fraction can reflect greater tumor DNA shedding and has been associated with higher tumor burden, metastatic disease, and poorer prognosis.[36] Consequently, liquid biopsy specimens collected at different time points can have variable ctDNA levels and assay results. A low tumor fraction increases the risk of a false-negative result and of missing an acquired *ESR1* mutation because of limited tumor material in the specimen. ctDNA test results from specimens with low tumor fractions should be interpreted with caution. In addition, NGS-based ctDNA testing varies across clinical laboratories in sequencing depth, gene panel size, and alteration-specific detection thresholds.

In summary, while highly sensitive digital polymerase chain reaction and comprehensive NGS panels have made ctDNA testing a useful tool for longitudinal disease monitoring and early resistance detection, the approach retains important limitations. A key limitation is the variability of tumor fractions in the blood, where low ctDNA shedding can cause false-negative results that obscure *ESR1* mutations. Guidelines from the National Comprehensive Cancer Network recommend careful interpretation of low-fraction samples and repeat liquid biopsy or tissue biopsy to ensure accurate therapeutic planning.[37]

ESR1 genomic alterations beyond hotspot missense mutations

Although hotspot LBD point mutations are the best-established clinically actionable *ESR1* alterations, the clinical significance of non-hotspot *ESR1* alterations remains uncertain, and comparative data on their effects on treatment resistance are limited. In addition, other types of alterations, such as *ESR1* copy-number loss, amplification, and fusion, have also been detected in endocrine-resistant metastatic breast cancer but are less well studied.[38]

ESR1 amplification, reported in approximately 5–20% of hormone receptor-positive breast cancers by different studies, results in increased ER expression and enhanced estrogen signaling.[25] While *ESR1* amplification may contribute to endocrine sensitivity in some tumors, it has also been associated with adaptive resistance through persistent ER pathway activation despite estrogen deprivation. The clinical significance of *ESR1* amplifications in early-stage and recurrent disease is still under investigation.[39]

ESR1 fusions have been estimated to occur in 1–10% of hormone receptor-positive breast cancers by different studies.[40] Recurrent fusions often contain the first 1–6 exons of the *ESR1* gene, which encode the activation-function and DNA-binding domains but lack the ligand-binding domain and are fused in frame to various 3′ partner genes. These fusion proteins can be constitutively active and ligand-independent, and the loss of the ligand-binding domain may make tumors less sensitive to therapies that require binding to the ER LBD.[41]

Although these alterations are relatively rare compared with *ESR1* missense mutations and may be less readily detected by early-generation liquid biopsy assays, their reported detection is increasing as comprehensive NGS assays incorporating copy-number analysis and RNA sequencing for fusions are used more frequently in metastatic settings. Unlike *ESR1* hotspot mutations, which currently guide the use of next-generation SERDs, SERMs, and PROTACs, the clinical significance of *ESR1* amplifications and fusions is not yet fully understood and is under active investigation.

The evolving role of pathologists in *ESR1* testing

Recent advances and emerging therapies, together with guidelines recommending *ESR1* mutation testing at recurrence or progression, emphasize the evolving role of pathologists within the multidisciplinary breast cancer team. In the era of precision medicine, pathologists contribute to personalized patient care through diagnosis and by guiding molecular testing strategies and interpreting complex biomolecular data. The role of pathologists has expanded beyond diagnosis to broader participation throughout the clinical care pathway. By understanding ER signaling, *ESR1* biology, and the application of *ESR1* mutation testing, including liquid biopsy, pathologists' responsibilities now include supporting decisions about the optimal timing and modality for *ESR1* mutation testing, advising on plasma versus tissue sample selection, and facilitating communication of molecular test results within the care team.

Limitations

As a mini review, the major limitations include its narrative approach and the potential for literature-selection bias. The rapid evolution of evidence and regulatory guidance in this area may mean that some recent advances are not fully captured. Additionally, heterogeneity among ctDNA testing platforms and the relatively limited data on non-hotspot *ESR1* alterations may restrict the generalizability and comprehensiveness of the conclusions drawn. Future systematic reviews and meta-analyses could strengthen the evidence base and further clarify the clinical utility of *ESR1* testing.

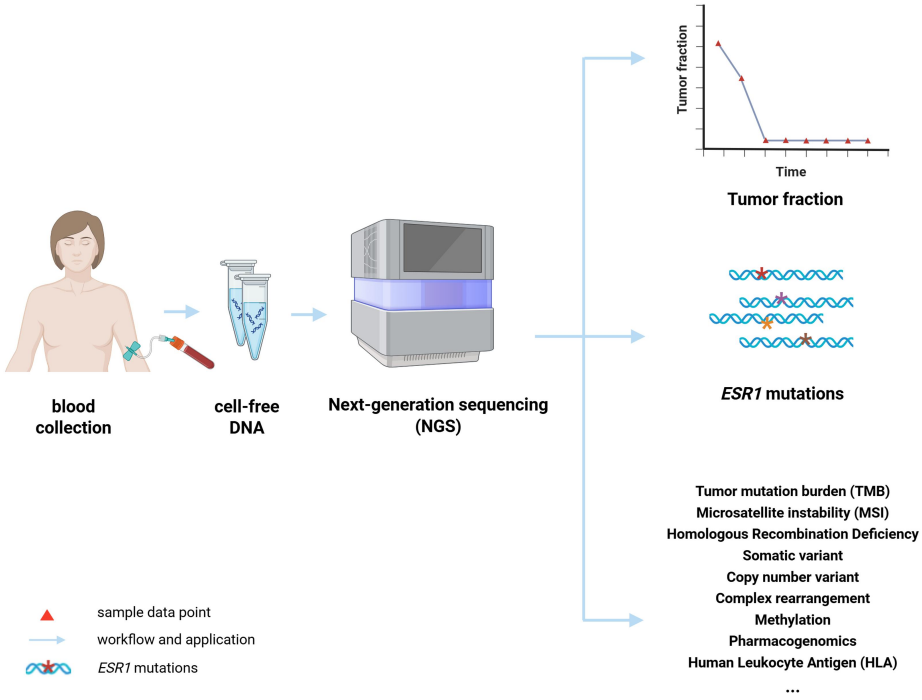

Fig. 2. Liquid biopsy testing in breast cancer. Peripheral blood is drawn into specialized collection tubes that stabilize cell-free DNA (cfDNA), after which cfDNA is extracted and subjected to next-generation sequencing (NGS). This approach provides contemporaneous information on tumor fraction, *ESR1* mutations, and other cancer biomarkers. Created with BioRender.com. HLA, human leukocyte antigen; MSI, microsatellite instability; TMB, tumor mutation burden.

Conclusions

ERα signaling is a key driver of the development and progression of hormone receptor-positive/HER2-negative breast cancers, while acquired *ESR1* alterations are a major mechanism of endocrine resistance. Liquid biopsy is now an established clinical approach to *ESR1* testing in advanced or metastatic hormone receptor-positive/HER2-negative breast cancer, including at recurrence or progression during endocrine therapy and, in selected patients, during ongoing aromatase inhibitor plus CDK4/6 inhibitor therapy to detect emerging *ESR1* mutations. It is also being investigated for recurrence prediction and treatment monitoring. However, the regulatory landscape for liquid biopsies and targeted therapies is evolving rapidly. As new targeted therapies and companion diagnostics are developed, the role of liquid biopsy may continue to expand. Pathologists should remain current with advances relevant to their supporting role in multidisciplinary breast cancer care.

Acknowledgments

None.

Funding

No funding was received for this review.

Conflict of interest

YW is an Editorial Board Member of the *Journal of Clinical and Translational Pathology*. LL has no conflicts of interest to disclose.

Author contributions

Drafting the manuscript (LL, YW); critical revision of the manuscript (LL, YW). Both authors made significant contributions to this review and approved the final manuscript.

References

[1] Arendt LM, Kuperwasser C. Form and function: how estrogen and progesterone regulate the mammary epithelial hierarchy. J Mammary Gland Biol Neoplasia 2015;20(1-2):9–25. DOI: 10.1007/s10911-015-9337-0, PMID: 26188694.

[2] Beatson GT. On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases. Trans Med Chir Soc Edinb 1896;15:153–179. PMID: 29584099.

[3] Jensen EV, Desombre ER, Hurst DJ, Kawashima T, Jungblut PW. Estrogen-receptor interactions in target tissues. Arch Anat Microsc Morphol Exp 1967;56(3):547–569. PMID: 5615176.

[4] Puhalla S, Bhattacharya S, Davidson NE. Hormonal therapy in breast cancer: a model disease for the personalization of cancer care. Mol Oncol 2012;6(2):222–236. DOI: 10.1016/j.molonc.2012.02.003, PMID: 22406404.

[5] Krauss K, Stickeler E. Endocrine Therapy in Early Breast Cancer. Breast Care (Basel) 2020;15(4):337–346. DOI: 10.1159/000509362, PMID: 32982643.

[6] Campone M, De Laurentiis M, Jhaveri K, Hu X, Ladoire S, Patsouris A, *et al*. Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Advanced Breast Cancer. N Engl J Med 2025;393(6):556–568. DOI: 10.1056/NEJMoa2505725, PMID: 40454645.

[7] Bidard FC, Mayer EL, Park YH, Janni W, Ma C, Cristofanilli M, *et al*. First-Line Camizestrant for Emerging ESR1-Mutated Advanced Breast Cancer. N Engl J Med 2025;393(6):569–580. DOI: 10.1056/NEJMoa2502929, PMID: 40454637.

[8] Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, *et al*. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2023;388(22):2058–2070. DOI: 10.1056/NEJMoa2214131, PMID: 37256976.

[9] Basu GD, Innis PE, Deem AK, Starodynov A, Udhane SS, Szelinger S, *et al*. Characterization of ESR1 alterations in patients with breast and gynecologic cancers. Breast Cancer Res 2026;28(1):40. DOI: 10.1186/s13058-025-02217-0, PMID: 41555446.

[10] Miller TW, Balko JM, Fox EM, Ghazoui Z, Dunbier A, Anderson H, *et al*. ERα-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer. Cancer Discov 2011;1(4):338–351. DOI: 10.1158/2159-8290.CD-11-0101, PMID: 22049316.

[11] Robert NJ. Clinical efficacy of tamoxifen. Oncology (Williston Park) 1997;11(2 Suppl 1):15–20. PMID: 9065922.

[12] Osborne CK, Wakeling A, Nicholson RI. Fulvestrant: an oestrogen receptor antagonist with a novel mechanism of action. Br J Cancer 2004;90 Suppl 1(Suppl 1):S2–S6. DOI: 10.1038/sj.bjc.6601629, PMID: 15094757.

[13] Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. NPJ Breast Cancer 2023;9(1):20. DOI: 10.1038/s41523-023-00523-4, PMID: 37019913.

[14] Ferraro E, Walsh EM, Tao JJ, Chandarlapaty S, Jhaveri K. Accelerating drug development in breast cancer: New frontiers for ER inhibition. Cancer Treat Rev 2022;109:102432. DOI: 10.1016/j.ctrv.2022.102432, PMID: 35839531.

[15] Corti C, De Angelis C, Bianchini G, Malorni L, Giuliano M, Hamilton E, *et al*. Novel endocrine therapies: What is next in estrogen receptor positive, HER2 negative breast cancer? Cancer Treat Rev 2023;117:102569. DOI: 10.1016/j.ctrv.2023.102569, PMID: 37146385.

[16] U. S. Food and Drug Administration. FDA approves imlunestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. 2025. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-imlunestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast. Accessed May 28, 2026.

[17] U. S. Food and Drug Administration. FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. 2023. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer. Accessed May 28, 2026.

[18] Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, *et al*. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol 2022;40(28):3246–3256. DOI: 10.1200/JCO.22.00338, PMID: 35584336.

[19] Jhaveri KL, Neven P, Casalnuovo ML, Kim SB, Tokunaga E, Aftimos P, *et al*. Imlunestrant with or without Abemaciclib in Advanced Breast Cancer. N Engl J Med 2025;392(12):1189–1202. DOI: 10.1056/NEJMoa2410858, PMID: 39660834.

[20] U. S. Food and Drug Administration. FDA approves vepdegestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. 2026. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-vepdegestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast. Accessed September 8, 2026.

[21] Astor L. FDA Grants Lasofoxifene Fast Track Designation for ER+/ESR1-Mutant Metastatic Breast Cancer. 2019. Available from: https://www.onclive.com/view/fda-grants-lasofoxifene-fast-track-designation-for-eresr1mutant-metastatic-breast-cancer. Accessed May 28, 2026.

[22] Goetz MP, Bagegni NA, Batist G, Brufsky A, Cristofanilli MA, Damodaran S, *et al*. Lasofoxifene versus fulvestrant for ER+/HER2- metastatic breast cancer with an ESR1 mutation: results from the randomized, phase II ELAINE 1 trial. Ann Oncol 2023;34(12):1141–1151. DOI: 10.1016/j.annonc.2023.09.3104, PMID: 38072514.

[23] U. S. Food and Drug Administration. FDA grants accelerated approval to camizestrant with a CDK4/6 inhibitor for ESR1-mutated HR-positive, HER2-negative locally advanced or metastatic breast cancer. 2026. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-camizestrant-cdk46-inhibitor-esr1-mutated-hr-positive-her2-negative. Accessed September 11, 2026.

[24] Robinson DR, Wu YM, Vats P, Su F, Lonigro RJ, Cao X, *et al*. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 2013;45(12):1446–1451. DOI: 10.1038/ng.2823, PMID: 24185510.

[25] Jeselsohn R, Buchwalter G, De Angelis C, Brown M, Schiff R. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol 2015;12(10):573–583. DOI: 10.1038/nrclinonc.2015.117, PMID: 26122181.

[26] Reinert T, Saad ED, Barrios CH, Bines J. Clinical Implications of ESR1 Mutations in Hormone Receptor-Positive Advanced Breast Cancer. Front Oncol 2017;7:26. DOI: 10.3389/fonc.2017.00026, PMID: 28361033.

[27] Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res 2021;23(1):85. DOI: 10.1186/s13058-021-01462-3, PMID: 34392831.

[28] Betz M, Massard V, Gilson P, Witz A, Dardare J, Harlé A, *et al*. ESR1 Gene Mutations and Liquid Biopsy in ER-Positive Breast Cancers: A Small Step Forward, a Giant Leap for Personalization of Endocrine Therapy? Cancers (Basel) 2023;15(21):5169. DOI: 10.3390/cancers15215169, PMID: 37958343.

[29] Magbanua MJM, Ahmed Z, Sayaman RW, Brown Swigart L, Hirst GL, Yau C, *et al*. Cell-free DNA Concentration as a Biomarker of Response and Recurrence in HER2-Negative Breast Cancer Receiving Neoadjuvant Chemotherapy. Clin Cancer Res 2024;30(11):2444–2451. DOI: 10.1158/1078-0432.CCR-23-2928, PMID: 38470545.

[30] Nader-Marta G, Monteforte M, Agostinetto E, Cinquini M, Martins-Branco D, Langouo M, *et al*. Circulating tumor DNA for predicting recurrence in patients with operable breast cancer: a systematic

review and meta-analysis. ESMO Open 2024;9(3):102390. DOI: 10.1016/j.esmoop.2024.102390, PMID: 38460249.

[31] Bhave MA, Quintanilha JCF, Tukachinsky H, Li G, Scott T, Ross JS, *et al*. Comprehensive genomic profiling of ESR1, PIK3CA, AKT1, and PTEN in HR(+)HER2(-) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. Breast Cancer Res Treat 2024; 207(3):599–609. DOI: 10.1007/s10549-024-07376-w, PMID: 38872062.

[32] Bidard FC, Hardy-Bessard AC, Dalenc F, Bachelot T, Pierga JY, de la Motte Rouge T, *et al*. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2022; 23(11):1367–1377. DOI: 10.1016/S1470-2045(22)00555-1, PMID: 36183733.

[33] Turner NC, Mayer EL, Park YH, Janni W, Ma C, Cristofanilli M, *et al*. Switching to camizestrant at ESR1 mutation emergence before disease progression during first-line treatment of hormone receptor-positive advanced breast cancer (SERENA-6): extended analysis of a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Oncol 2026;27(8):941–958. DOI: 10.1016/S1470-2045(26)00287-1, PMID: 42442380.

[34] Burstein HJ, DeMichele A, Somerfield MR, Henry NL, Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels. Testing for ESR1 Mutations to Guide Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol 2023;41(18): 3423–3425. DOI: 10.1200/JCO.23.00638, PMID: 37196213.

[35] Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, *et al*. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2022;33(8): 750–768. DOI: 10.1016/j.annonc.2022.05.520, PMID: 35809752.

[36] Reichert ZR, Morgan TM, Li G, Castellanos E, Snow T, Dall'Olio FG, *et al*. Prognostic value of plasma circulating tumor DNA fraction across four common cancer types: a real-world outcomes study. Ann Oncol 2023;34(1):111–120. DOI: 10.1016/j.annonc.2022.09.163, PMID: 36208697.

[37] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 4.2026). Plymouth Meeting, PA: National Comprehensive Cancer Network; 2026. Available from: https://www.nccn.org. Accessed August 6, 2026.

[38] Razavi P, Chang MT, Xu G, Bandlamudi C, Ross DS, Vasan N, *et al*. The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers. Cancer Cell 2018;34(3):427–438.e6. DOI: 10.1016/j.ccell.2018.08.008, PMID: 30205045.

[39] Liu L, Graff SL, Cheng L, Wang Y. Paired Tissue and Circulating Tumor DNA Profiling Reveals Novel ESR1 Amplifications and CDK4/6 Inhibitor Resistance Mechanisms in Hormone Receptor-Positive/HER2-Negative Metastatic Breast Cancers. Lab Invest 2026;106(7): 106135. DOI: 10.1016/j.labinv.2026.106135, PMID: 42162670.

[40] Gou X, Kim BJ, Anurag M, Lei JT, Young MN, Holt MV, *et al*. Kinome Reprogramming Is a Targetable Vulnerability in ESR1 Fusion-Driven Breast Cancer. Cancer Res 2023;83(19):3237–3251. DOI: 10.1158/0008-5472.CAN-22-3484, PMID: 37071495.

[41] Nagy Z, Jeselsohn R. ESR1 fusions and therapeutic resistance in metastatic breast cancer. Front Oncol 2022;12:1037531. DOI: 10.3389/fonc.2022.1037531, PMID: 36686845.