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Opinion Paper

Bridging the Gap in Breast Cancer Care for LMICs: Cost-effective PCR-based testing as an alternative to the ctDNA sequencing method to detect ESR1 mutation

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Abstract

Breast cancer is the most common cancer among women worldwide, with disproportionately high mortality in low- and middle-income countries (LMICs) due to delays in diagnosis and limited access to treatment. In countries such as Pakistan, breast cancer tends to present at a younger age and is associated with poorer survival outcomes. Precision oncology approaches are needed to guide treatment, particularly for hormone receptor (HR)-positive, HER2-negative advanced breast cancer, where estrogen receptor 1 (ESR1) mutations drive endocrine resistance.
Selective estrogen receptor degraders (SERDs) improve outcomes when ESR1 mutations are detected early, yet circulating tumor DNA (ctDNA) sequencing, the standard testing method, is costly and infrastructure-dependent. Polymerase chain reaction (PCR)-based methods, especially droplet digital PCR (ddPCR), offer a sensitive, affordable, and scalable alternative. Adopting PCR-based ESR1 testing in LMICs can enable timely therapeutic switching, reduce ineffective treatment, and improve survival outcomes. This approach represents a practical pathway to precision oncology in resource-limited healthcare systems.

Keywords: Breast cancer, ESR1 mutation, PCR-based testing, ctDNA sequencing, LMICs, Cost-effectiveness, Precision oncology

1. Main Text

Breast cancer remains a major global health concern. In 2022, it was responsible for 670,000 deaths and affected 2.3 million women worldwide. It remains the most common cancer among women in 157 out of 185 countries [1]. While high-income nations report the highest number of new cases, the burden of mortality is increasingly falling on low- and middle-income countries (LMICs), where survival outcomes are significantly poorer. This discrepancy is mirrored by the considerable differences in outcomes based on a country's level of development. In high Human Development Index (HDI) countries, approximately 1 in 12 women are diagnosed with breast cancer during their lifetime, with 1 in 71 losing their lives to the disease. In comparison, in low-HDI countries, around 1 in 27 women receive a diagnosis, while 1 in 48 die from it [1]. These figures suggest that limited access to early detection, timely diagnosis, and effective treatment may significantly influence survival outcomes in resource-limited settings.

In Pakistan, women face a disproportionately high burden of cancer, with breast cancer being the most common. It accounts for 16.5% of all cases and has an age-standardized incidence rate of 34.2 per 100,000 [2]. However, the true burden is likely underestimated because of diagnostic limitations and incomplete data reporting. Breast cancer affects around 1 in 9 women in Pakistan, reflecting the notably high incidence of the disease. [3, 4] Moreover, the average age at diagnosis is 51.4

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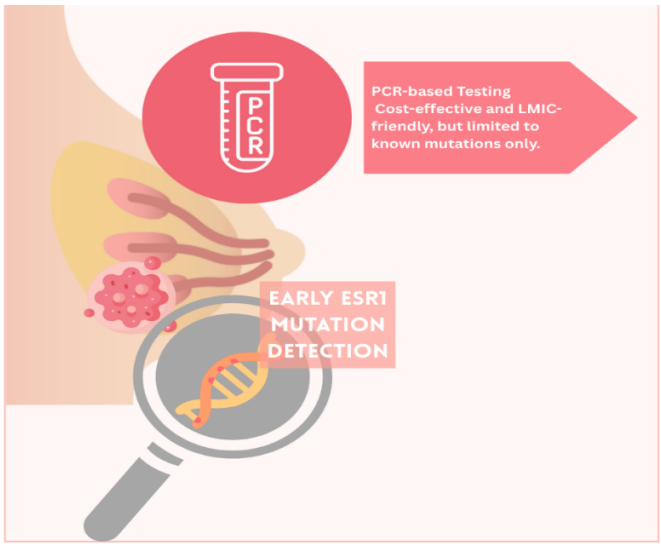

Graphical Abstract: *Cost-effective PCR-based detection of ESR1 mutations as an accessible alternative to ctDNA sequencing for improving breast cancer care in Lower- and Middle-Income Class (LMICs)*

years, nearly a decade earlier than the average age of 61 among white American women [5]. This earlier onset, coupled with delays in diagnosis and treatment, contributes to poorer outcomes and highlights the urgent need for equitable cancer care.

Against this backdrop, precision oncology tools that support personalized treatment strategies are urgently needed in LMICs. However, many such tools remain inaccessible due to cost and infrastructure barriers. Patients with advanced or recurrent stage IV hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer without visceral crisis are commonly treated with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor combined with endocrine therapy, typically an aromatase inhibitor or, in selected settings, fulvestrant. This treatment approach is considered a standard of care (SOC), with clinical trials such as MONALEESA-2, PALOMA-2, and MONARCH-3 demonstrating significant survival benefits with CDK4/6 inhibitor-based therapy [6–8]. Fulvestrant-based endocrine therapy, with or without CDK4/6 inhibition, is another option for selected patients, as shown in trials such as MONALEESA-3 and FACT [9, 10]. Additionally, in rare circumstances, patients with advanced HR-positive disease and HER2-activating mutations may find a combination of endocrine therapy (ET) plus a HER2-targeted drug (such as trastuzumab or neratinib) an acceptable option.

Although estrogen receptor 1 (ESR1) activating mutations are a well-established mechanism of acquired endocrine resistance in metastatic disease, they are rare in treatment-naïve primary tumors by standard sequencing (1%); ultra-sensitive assays (locked nucleic acid [LNA]-clamp ddPCR or high-sensitivity ddPCR) can detect ultra-low-frequency ESR1 clones in a subset of primary cancers, but the prognostic significance of these tiny clones with variant allele frequencies (VAFs) <0.1% remains unproven [11–13]. Subsequently, when a patient's cancer fails to respond to a given line of endocrine therapy (ET), it is essential to consider whether the patient has developed ESR1-mediated resistance. Hence, in such cases, these patients may benefit from a selective estrogen receptor degrader (SERD) such as elacestrant. With recent advancements in molecular studies and more clinical data, testing for ESR1 mutations is now becoming a standard approach to guide treatment in HR-positive breast cancer patients. ESR1 testing has prognostic and predictive implications. Figure 1 illustrates the molecular basis of ESR1 mutations alongside key clinical trials testing SERD-based strategies, highlighting how biological insights are being translated directly into therapeutic interventions.

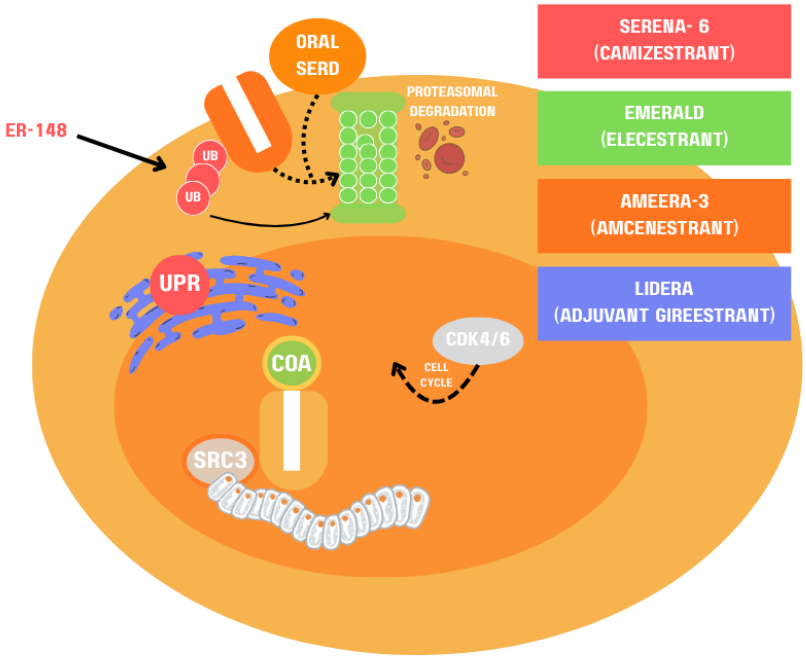

Figure 1: *Overview of oral selective estrogen receptor degraders (SERDs) targeting ESR1 mutations, illustrating receptor ubiquitination, proteasomal degradation, and downstream effects on coactivator binding, unfolded protein response, and CDK4/6-regulated cell-cycle progression. Key clinical trials of next-generation SERDs include SERENA-6 (camizestrant), EMERALD (elacestrant), AMEERA-3 (amcenestrant), and LIDERA (adjuvant gireestrant).*

Recent findings from the SERENA-6 phase III clinical trial in the setting of first-line treatment have demonstrated a promising new approach to managing endocrine resistance in patients with HR-positive, HER2-negative advanced breast cancer. The study focused on the early detection of ESR1 mutations, genetic changes associated with resistance to aromatase inhibitors, through regular monitoring of circulating tumor DNA (ctDNA). After identifying these mutations, patients were switched from standard endocrine therapy to camizestrant, an oral SERD [14]. Patients who transitioned to camizestrant experienced a final median progression-free survival (PFS) of 16.8 months, compared with 9.2 months in those who continued on aromatase inhibitors (hazard ratio, 0.45; 95% CI, 0.34–0.59), a 55% reduction in the risk of progression or death [14]. The trial also met its key secondary endpoint of time to progression on the next line of therapy (PFS2), with a hazard ratio of 0.63 (95% CI, 0.46–0.86; P=0.00373) favoring early switching [15]. Moreover, in the EMERALD study, elacestrant was compared with the SOC endocrine treatment in HR-positive HER2-negative advanced breast cancer patients who progressed after CDK4/6 inhibitors and chemotherapy. Elacestrant improved PFS compared with SOC in patients with ESR1 mutations; however, the overall survival (OS) endpoint was not met, with a hazard ratio of 0.90 (95% CI, 0.63–1.30), indicating no statistically significant OS benefit [16]. Therefore, selecting treatment based on ESR1 mutation status may help overcome endocrine resistance and improve disease control in HR-positive breast cancer. Table 1 summarizes selected recent and ongoing studies, including their setting, disease biology, trial stage, primary endpoints, and anticipated completion dates.

Table 1: Summary of key clinical trials evaluating next-generation oral SERDs across advanced and early HR+/HER2– breast cancer settings

NCT Number/ Trial Name	Stage/ Setting	Primary Outcome	Key Findings
NCT04964934/ SERENA-6 (Camizestrant)	Advanced/Switching at ESR1 emergence	PFS	mPFS 16.8 vs 9.2 months (HR 0.45) favoring camizestrant switch; PFS2 25.7 vs 19.1 months (HR 0.63, 95% CI 0.46–0.86; P=0.00373)
NCT03778931/ EMERALD (Elacestrant)	Advanced/post-ET	PFS (overall + ESR1 subgroup)	Elacestrant improved PFS vs SOC ET; Greater benefit in ESR1-mutant subgroup
NCT04059484/ AMEERA-3 (Amcenestrant Monotherapy)	Advanced/post-ET	PFS	No PFS benefit overall (3.6 vs 3.7 mo, hazard ratio 1.05)
NCT04576455/ acelERA (Giredestrant)	Advanced/Previously treated (1-2 prior lines)	PFS	Did not meet primary PFS (HR 0.81); ESR1-mutant subset mPFS 5.3 vs 3.5 mo (hazard ratio 0.60).
NCT04961996/ lidERA (Adjuvant Giredestrant)	Adjuvant (early operable)	IDFS	Significantly improved IDFS vs standard endocrine therapy (HR 0.70, 95% CI 0.57–0.87; P=0.0014); 3-year IDFS 92.4% vs 89.6%. DRFI also favored giredestrant (HR 0.69, 95% CI 0.54–0.89). Interim OS showed a nonsignificant trend (HR 0.79, 95% CI 0.56–1.12)

PFS: progression-free survival; PFS2: second progression-free survival; OS: overall survival; mPFS: median progression-free survival; CI: confidence interval; IDFS: invasive disease-free survival; ET: endocrine therapy; DRFI: distant recurrence-free interval.

ESR1 mutations can be tested either in tumor tissue using next-generation sequencing (NGS) or in blood using circulating tumor DNA (ctDNA) assays. The most common ctDNA methods are droplet digital PCR (ddPCR) for hotspot mutations and targeted NGS panels for broader profiling. However, implementing these innovations in clinical practice in LMICs presents significant challenges. High costs, limited access to ctDNA sequencing, and the financial burden of therapies like camizestrant often make this approach inaccessible in resource-limited settings. In this context, polymerase chain reaction (PCR)-based methods offer a more viable alternative for detecting ESR1 mutations. PCR is significantly more affordable and compatible with existing laboratory infrastructure in LMICs, making it a practical option for integrating molecular monitoring into breast cancer care. By adopting PCR as a surveillance tool, LMICs may adapt aspects of the SERENA-6 strategy, enabling earlier intervention and improved outcomes while broader access to advanced therapies continues to develop.

Technologies such as droplet digital PCR (ddPCR) provide a practical and affordable alternative for detecting ESR1 mutations. These platforms are compatible with equipment already used in many LMICs for infectious disease diagnostics, including tuberculosis and HIV viral load monitoring. ddPCR has shown high sensitivity in identifying key ESR1 mutations associated with endocrine resistance, such as E380Q, D538G, and Y537S [17, 18]. This method can detect even low-frequency mutations and identify multiple concurrent alterations in a single reaction, enhancing its clinical utility. Importantly, rising ESR1 mutation levels detected through longitudinal PCR monitoring have been associated with treatment resistance and can serve as early indicators for therapeutic adjustment [17, 18].

In clinical practice, the turnaround time from blood draw to result determines how quickly a therapeutic switch can be made. The ddPCR assay itself is rapid, allowing same-day processing once plasma is available. However, real-world data from the PADA-1 trial, which used a comparable single-tube ddPCR platform for prospective ESR1 monitoring across 83 centers, reported a median turnaround time from blood draw to result notification of 13 days, with sample transport to the central laboratory accounting for a median of 1 day. Notably, the turnaround time improved substantially with process maturation, from a median of 32 days in 2017 to 8 days in 2021, suggesting that logistics and workflow optimization, rather than assay chemistry, are the primary determinants of real-world turnaround time [19].

For LMIC implementation, establishing regional laboratories with dedicated workflows could therefore target a clinically actionable turnaround time of approximately 1–2 weeks. Further decentralization and workflow optimization could shorten this interval. A sufficiently rapid reporting pathway is essential because the benefit of an ESR1-guided treatment switch depends on identifying resistance before radiographic progression and initiating alternative therapy without prolonged continuation of ineffective endocrine treatment.

Given its affordability, speed, and minimal infrastructure requirements, ddPCR represents a viable option for LMICs to adopt molecular surveillance strategies, potentially enabling timely treatment interventions similar to those seen in the SERENA-6 and EMERALD trials.

Implementation of PCR-based ESR1 testing in LMICs could follow a tiered strategy. First, testing may be introduced in metastatic breast cancer patients undergoing endocrine therapy, particularly when clinical or biochemical indicators of resistance appear, even in the absence of radiographic progression. Second, establishing centralized regional laboratories equipped with ddPCR offers a cost-effective alternative. These labs can process blood samples from peripheral clinics, enabling

high-sensitivity detection of ESR1 mutations while reducing the need for expensive infrastructure at every point of care. Third, integrating ESR1 mutation testing into national breast cancer guidelines and reimbursement schemes is essential. Cost sustainability could be supported through the pooled procurement of reagents, local production of PCR kits, and workforce training.

From a cost-effectiveness perspective, broad ctDNA sequencing can impose substantial costs, with reported per-test costs ranging from approximately USD 800–1,500 in some clinical and economic analyses [20, 21]. In contrast, ddPCR assays for ESR1 hotspots have been reported at substantially lower per-sample costs [22], potentially making them more feasible in resource-constrained settings. Economic models of elacestrant suggest incremental cost-effectiveness ratios (ICERs) as high as USD 380,000 per quality-adjusted life-year (QALY) at current drug prices [23], highlighting that test-and-treat value depends not only on assay cost but also on drug affordability. A simple LMIC-relevant model would compare usual care versus periodic ddPCR surveillance with an ESR1-guided SERD switch, using local inputs such as ESR1 prevalence (20-30%) in AI-pretreated metastatic cohorts, test cost, and negotiated SERD prices. Outputs would include incremental cost per QALY and budget impact, enabling policymakers to decide whether ddPCR surveillance is economically sustainable [24]. Figure 2 shows a stepwise approach to implementing cost-effective ESR1 testing in LMICs.

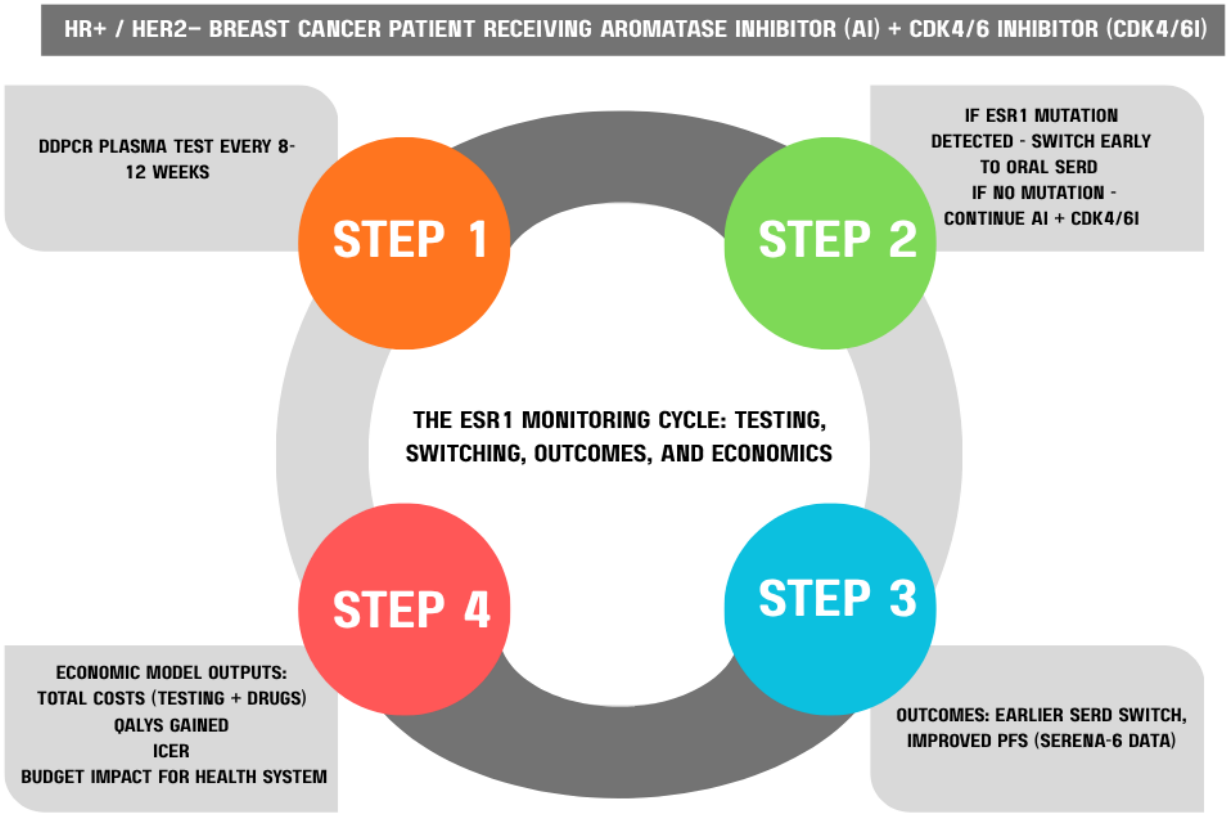

Figure 2: *The ESR1 monitoring cycle for HR+/HER2– breast cancer patients receiving aromatase inhibitor therapy with CDK4/6 inhibition. The cycle outlines four key steps (1) proposed routine ddPCR plasma testing every 8–12 weeks; (2) treatment decision-making based on ESR1 mutation status, including early switch to an oral SERD when detected; (3) clinical outcomes associated with earlier switching, such as improved progression-free survival; and (4) economic evaluation incorporating testing costs, drug costs, QALYs gained, ICER, and overall budget impact for health systems.*

2. Conclusion

Looking ahead, as oral SERDs become more accessible globally, including the potential for generic versions, PCR-based testing for ESR1 mutations could become routine care in LMICs. This could enable timely therapeutic switching and reduce prolonged exposure to ineffective endocrine therapy, potentially improving clinical outcomes. In conclusion, while

ctDNA-guided therapy is still evolving in many parts of the world, PCR-based ESR1 mutation testing offers a feasible and impactful entry point for precision oncology in LMICs. With targeted investment, policy integration, and public-private collaboration, this approach can bridge the gap in cancer care and deliver personalized treatment strategies to women most in need.

3. Abbreviations

The following abbreviations are used in this manuscript:

LMICs	Low- and middle-income countries
ESR1	Estrogen receptor 1
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
CDK4/6	Cyclin-dependent kinase 4/6
SOC	Standard of care
ET	Endocrine therapy
LNA	Locked nucleic acid
ddPCR	Droplet digital polymerase chain reaction
SERD	Selective estrogen receptor degrader
PFS	Progression-free survival
PFS2	Second progression-free survival
OS	Overall survival
CI	Confidence interval
NGS	Next-generation sequencing
VAF	Variant allele frequency
PCR	Polymerase chain reaction
ICER	Incremental cost-effectiveness ratio
QALY	Quality-adjusted life-year
IDFS	Invasive disease-free survival
DRFI	Distant recurrence-free interval

Author Bio

Saqib Raza Khan is a Medical Oncologist and Thoracic Fellow at the London Health Sciences Center, LRCP, Ontario, Canada. He and his co-authors advocate for evidence-informed, outcomes-based integration of affordable testing in LMICs to enable timely therapeutic management and a practical pathway to precision oncology in resource-limited healthcare systems.

Author Contributions

The authors conceived the editorial argument, synthesized the supporting literature, and drafted the manuscript.All authors declare no conflict of interest.

Use of Artificial Intelligence

The authors confirm that no content in this manuscript was generated using artificial intelligence (AI) tools, and the authors take full responsibility for the accuracy and integrity of the work.

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