Advancing Precision Medicine: Integrating ESR1 Mutation Testing into Oncology Practices

INTRODUCTION

ESR1 mutations act as critical drivers of endocrine resistance in hormone receptor positive (HR+) HER2 negative (HER2-) metastatic breast cancer (mBC) by enabling estrogen-independent activation and constant signaling of estrogen receptors, particularly the estrogen receptor alpha (ERα).[1] These mutations are primarily acquired under the selective pressure of aromatase inhibitor (AI) treatments and are rare in primary tumors but significantly more common in metastatic breast cancer following following AI therapy.[2]

After adjuvant AI therapy, 4-5% of patients display acquired ESR1 mutations, a figure that rises to 20-40% in metastatic scenarios, and potentially up to 50% in later treatment stages.[3] These mutations correlate with poorer overall survival and progression-free survival, indicating a more aggressive disease course.[4] Clinically, identifying ESR1 mutations is crucial for guiding biomarker-driven treatment selection, including the selective estrogen receptor degrader elacestrant, and determining prognosis.[4,5] ASCO recommends testing for these mutations at recurrence or progression on endocrine therapy in HR+/HER2- mBC. Per their expert panel, patients who remain ESR1 wild-type may benefit from retesting at each subsequent progression on endocrine therapy to see if a mutation has arisen.[6]

Unlike stable mutations like PIK3CA, ESR1 mutations are subclonal and heterogeneous. In this case, blood-based circulating tumor DNA (ctDNA) testing tends to be more sensitive than tissue biopsies, which may not detect these mutations.[7,8] The Guardant360® CDx is an FDA-approved test to determine ESR1 mutation status in breast cancer; however, there may be other tests with different methodologies like Next Generation Sequencing (NGS) or Droplet Digital Polymerase Chain Reaction (ddPCR) that claim ESR1 coverage.[9] Importantly, primary archived breast cancer tissue should not be used as a source of tumor testing for ESR1 mutations as patients' ESR1 mutation status is likely to change over time depending on sequence of therapies.[11]

EXPLORING ESR1 TESTING ACROSS DIVERSE ONCOLOGY PRACTICES

To better understand how ESR1 testing is currently integrated into various clinical settings, we interviewed medical oncologists and oncology pharmacists from three distinct oncology practice archetypes. Each represents a unique approach to incorporating new testing methodologies into the management of patient care:

1. Academic Specialist Practices: Large academic medical centers often lead the way in adopting cutting-edge methodologies, continually pushing the boundaries of oncology care. In these types of centers, oncologists and pharmacists generally practice within a specialty breast clinic. These specialists are not only deeply involved in patient care but are also on the forefront of research and subspecialty innovation. They play a key role in generating evidence and often contribute to the creation of national and institutional guidelines that shape oncology care across settings.

2. Community Specialist Practices: Representing part of the continuum of community oncology, these practices balance evidence-based care with thoughtful adoption of emerging technologies like ESR1 testing. These sites may have a main clinical hub with several regional satellite clinics. Oncologists and pharmacists may practice in a breast specialty clinic at the main facility, while regional community practitioners would see a mix of tumor types.

EXPLORING ESR1 TESTING ACROSS DIVERSE ONCOLOGY PRACTICES - CONT.

3. Community Generalist Practices: Care teams in community generalist practices likely manage a variety of tumor types daily. Grounded in proven, long-standing methods of cancer care, these practices emphasize consistency and patient-centered approaches while integrating new testing as resources and workflows allow.

Through these interviews, we examine the operational workflows, patient selection criteria, testing practices, and challenges faced by each practice type. We also explore how resources are utilized and discuss future directions for ESR1 testing adoption across the oncology landscape.

WORKFLOW AND PATIENT SELECTION

Academic Specialist Practices

Practitioners within the academic specialist practice remarked that mutational testing decisions are primarily driven by providers. Without strict algorithms dictating therapy or pathway protocols, these practices embrace a highly individualized, patient-specific approach. Providers may order tests in coordination with a restaging scan or preemptively based on emerging clinical symptoms.

Novel mutation-targeting therapies and any applicable companion diagnostic tests are reviewed during molecular tumor board meetings. In terms of ESR1 testing, the care team discussed relevant clinical data, how NGS screening comes into play, and management of ESR1 positivity with elacestrant.

While exploring the integration of testing workflows into electronic medical records (EMRs), potential downsides were highlighted. For instance, testing that is automatically triggered in an integrated EMR might prompt unnecessary testing in stable patients, such as those receiving CDK 4/6 inhibitors for extended periods. Given the high cost of NGS, testing is reserved for scenarios where actionable information is likely.

Community Specialist Practices

The interviewed community specialist practice follows internal clinical pathways that guide mutation testing after progression on first-line treatment. These pathways, maintained by oncology staff, are particularly useful for providers at regional sites who manage a broad range of tumor types. The pathways recommend considering NGS testing after initial progression to identify candidates for additional treatment options. This practice has a weekly molecular tumor board which convenes to review NGS screening results and possible next steps in therapy. It's a helpful forum to review complex patient cases especially when multiple mutations are found.

The institution uses an online clinical pathways system to support provider decision-making. Genomic profiling is integrated into this system, requiring clinicians to access a dedicated website when placing orders. The platform includes a molecular page listing relevant tests by cancer type, and within the breast cancer pathways—particularly for HR+/HER2- metastatic disease—there are embedded links for ordering genomic tests. Additionally, the platform features biomarker-specific pages for ESR1 mutations, as well as others, which serve as helpful reminders and educational tools for clinicians. These pathways, maintained by oncology staff, are particularly useful for providers at regional and more rural sites, who often manage a broad range of tumor types and may have less access to subspecialty resources. Clinical pathways and decision support technologies help ensure consistency, aiding in standardizing care across geographies and practice settings.

Community Generalist Practices

Community generalist practices typically rely on physician discretion for precision medicine testing, with minimal formal infrastructure. These practices may lack standardized staff education and often engage in informal physician discussions rather than structured committee meetings.

Decisions about precision medicine testing are left to individual physicians, each managing a diverse mix of patients. While clinical pathways may

WORKFLOW AND PATIENT SELECTION - CONT.

be used when required by insurance companies, there are no comprehensive internal guidelines for ESR1 testing. Testing protocols tend to be reactive rather than proactive, driven by immediate clinical needs rather than standardized processes.

Pharmacists in these settings, while not integrated into every clinic, often serve as liaisons for clinical needs and collaborate with nursing departments to refine best practices. The integration of pharmacists can support more cohesive workflows, particularly when managing precision medicine protocols. These practices reflect a pragmatic approach that balances testing utility with patient well-being. Providers express caution about over-standardizing testing, emphasizing the importance of considering each patient's unique journey. In some cases, they prioritize practical patient needs over tests with a low likelihood of yielding actionable results. Pharmacists, by fostering multidisciplinary discussions and contributing to education initiatives, can bridge the gap between traditional workflows and emerging precision medicine practices.

Across the three archetypes, ESR1 testing tends to be reserved for HR+/HER2- metastatic disease that has progressed on at least one line of hormone-based therapy. An exception to this may be testing for ESR1 in a patient who has progressed from localized to metastatic disease following adjuvant AI therapy. In this case, providers may screen for mutations at metastatic disease diagnosis as the patient has already had hormone therapy exposure. However, in the first line setting most providers wish to offer therapy with a combination of agents. Based on current data, ESR1 positivity would indicate monotherapy with an ESR1 targeted agent.

TESTING PRACTICES AND TIMING

Academic Specialist Practices

In academic specialist practices, ESR1 mutation testing is typically conducted upon disease progression, particularly after first-line treatment with CDK 4/6 inhibitors and endocrine therapy. Testing is generally performed using blood-based NGS unless tissue biopsy is specifically indicated.

Providers in these settings emphasize the importance of testing at each progression, particularly if the patient remains endocrine-sensitive. This testing practice is largely driven by the potential to identify actionable mutations that may influence subsequent treatment decisions. However, if a patient is no longer endocrine-sensitive or is transitioning to chemotherapy, which does not rely on endocrine pathways, ESR1 testing may be deprioritized.

Community Specialist Practices

In community specialist practices, ESR1 mutation testing is not typically performed at the initial diagnosis of HR+/HER2- mBC. Testing is more commonly conducted after disease progression, especially following treatment with AIs. In some cases, testing may also be considered during later stages of treatment, including chemotherapy, to explore potential therapeutic options. Blood-based molecular profiling is the predominant method for NGS screening in this practice as well, since there is a high level of trust that circulating tumor DNA (ctDNA) will capture targetable mutations. Providers in these settings approach ESR1 testing strategically, using it to inform therapy choices rather than conducting it routinely at every progression. Testing is often initiated during stable first-line therapy to establish a molecular profile that can guide future treatment decisions. The utility of ESR1 testing tends to diminish once patients transition to chemotherapy, though it may still be considered if there are limited treatment options.

The clinician within this practice type indicated they typically reserve ESR1 testing for later stages of treatment, particularly when considering IV therapies. Their experience with elacestrant shortly after its approval yielded limited results, prompting reflection on whether it might be more effective if introduced earlier in the treatment sequence. However, uncertainty around insurance coverage and treatment guidelines presents a barrier. They noted that by the time elacestrant is typically used, tumors are often highly endocrine-resistant, which may diminish the drug's effectiveness. This suggests that earlier ESR1 testing could help identify patients who might benefit from this therapy sooner.

Community Generalist Practices

Community generalist practices tend to approach ESR1 mutation testing

TESTING PRACTICES AND TIMING – CONT.

conservatively, focusing on cost-effectiveness and clinical utility. Testing is generally reserved for patients who have progressed on multiple lines of endocrine therapy, where the likelihood of identifying an actionable mutation is higher.

In these settings, pharmacists can play a crucial role in supporting testing decisions. While testing protocols are often left to physician discretion, pharmacists conducting chart reviews can flag patients who may benefit from ESR1 testing, ensuring that potential therapeutic options are not overlooked. This involvement helps bridge gaps in workflow and ensures that testing is considered even in practices without formalized precision medicine structures.

Providers in these settings emphasize the importance of making informed decisions based on available data. They are cautioned about testing too early in the metastatic setting, given the low incidence of ESR1 mutations in early-stage disease and the limited impact on treatment decisions at that stage. Testing is prioritized in scenarios where it is most likely to influence patient management.

Overall, while these practices recognize the value of ESR1 testing, they advocate for its judicious use, balancing the potential benefits with the financial and emotional costs to patients. Pharmacists' involvement in these workflows can enhance decision-making, ensuring a patient-centered, multidisciplinary approach.

Liquid biopsies, leveraging ctDNA, are the preferred method for ESR1 mutation testing at all three sites due to their non-invasive nature and sensitivity. Tissue biopsies are used when liquid samples are inadequate or when specific progression sites are targeted. However, archived tissue is not suitable, as ESR1 mutation status evolves with treatment.

RESOURCE UTILIZATION AND EDUCATION

Academic Specialist Practices

In academic specialist practices, communication with patients about ESR1 mutation testing is clear and integrated into discussions about personalized treatment. Patients are informed about how testing helps tailor therapies, particularly when drugs like elacestrant are considered following mutation identification.

Educational and Financial Support: Tumor boards serve as the primary platform for reviewing new drugs, diagnostics, and best practices. Pharmacists play a crucial role in championing the adoption of new practices, educating teams, and managing updates in testing protocols. The integration of new data is a collaborative process, with teams discussing how to implement changes in patient care.

Community Specialist Practices

In community specialist practices, patient communication about ESR1 testing is typically managed by providers, with additional counseling provided when actionable mutations are identified. Genetic counselors are primarily involved at diagnosis, particularly for hereditary mutations like BRCA, but likely play a limited role in later line acquired mutational testing such as ESR1.

Educational and Financial Support: Internal clinical pathways and weekly molecular tumor boards guide testing practices. However, there is a need for more detailed guidelines from organizations like NCCN or ASCO to standardize ESR1 testing practices, particularly regarding testing frequency and variant allele frequency (VAF) thresholds.

Community Generalist Practices

Community generalist practices rely on individual physicians to communicate the implications of ESR1 testing to patients, with no standardized approach across the practice. Precision medicine decisions are made at the physician's discretion, and patient discussions are tailored to individual clinical scenarios.

Pharmacists play a vital role in supporting education within these practices. They actively monitor updates in guidelines and new drug approvals, sharing relevant information with the pharmacy team and coordinating educational sessions with drug representatives when necessary. This informal yet effective process ensures that the pharmacy team remains up-to-date, even in the absence of a formal precision medicine infrastructure.

RESOURCE UTILIZATION AND EDUCATION - CONT.

Educational and Financial Support: Educational initiatives are limited by scheduling constraints, and there are no formal precision medicine guidelines in place. Informal physician discussions occur, but there is no structured process for updating staff on new testing protocols or best practices. Pharmacists help bridge this gap by sharing resources from organizations like NCODA and developing in-house materials for patient education.

KEY CONSIDERATIONS AND FUTURE NEEDS:

Expanded Testing:

Providers anticipate a future where ESR1 testing is integrated earlier in the treatment timeline, potentially at diagnosis or in the adjuvant setting. With advancements in targeted therapies, there is growing interest in tailoring endocrine therapy based on early mutation detection.

Complex Sequencing:

As new agents emerge, sequencing decisions become more intricate, necessitating robust clinical guidelines and decision-support tools.

Education:

Increasing awareness of ESR1 mutation dynamics among general oncologists is crucial to optimizing testing strategies.

Guideline Development:

There is a need for clearer guidance on testing frequency and application to support community oncologists in adopting precision medicine approaches.

Persistent Testing:

Testing at each disease progression, even in patients who were previously ESR1 wild type, will ensure those who develop mutant ESR1 are offered appropriate therapy.

Streamlined Processes:

Simplifying administrative tasks, such as insurance authorization and paperwork, will enhance testing feasibility.

EMR Optimization:

Organizations should consider leveraging EMR-integrated pathways and technology-driven decision support tools. Embedding biomarker testing alerts, including ESR1 testing, within EMR pathways can streamline decision-making and support timely testing.

Combination Therapy:

Providers should stay abreast of current clinical trials investigating combining elacestrant with other therapies. This could contribute to earlier use of ESR1 targeted therapies.

CONCLUSION

The integration of ESR1 mutation testing in metastatic hormone receptor-positive, HER2-negative breast cancer represents a dynamic, patient-centered evolution in precision oncology. While academic centers have led the charge with focused, up-to-date approaches, community settings face challenges in aligning with rapidly evolving standards due to resource constraints and broader oncologic responsibilities.

Disparities between academic and community practices highlight the need for simplified guidance, increased awareness, and robust educational support to ensure that all patients benefit from the latest advancements. Standardizing testing protocols and clarifying guidelines, particularly regarding testing frequency and application, can bridge these gaps, ensuring consistency across diverse care settings.

There is also a growing recognition of the potential role pharmacists could play in identifying patients who may benefit from ESR1 testing. Structured algorithms and electronic decision-support tools, if implemented, would enable pharmacists to contribute effectively during chart reviews, ensuring that necessary testing steps are completed. This collaboration could enhance the overall care model, aligning with the patient-centered philosophy of these practices.

Physicians and pharmacists also advocate for more guideline-supported recommendations for ESR1 testing. Such guidelines would facilitate uniform communication between pharmacy, nursing, and physician teams, ensuring consistency in patient care and enhancing multidisciplinary collaboration.

As therapies and diagnostics continue to advance, the role of ESR1 mutation testing will expand, with potential applications in earlier treatment stages, such as adjuvant therapy. The future of ESR1 testing lies in its ability to guide more personalized, effective treatment strategies, ultimately improving patient outcomes. Achieving this vision will require collaborative efforts across the oncology community to address systemic barriers, streamline processes, and prioritize precision medicine guided care care in both academic and community settings.

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