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Positive Quality Intervention: Estrogen Receptor 1 (ESR1) Mutation Testing in Metastatic, Hormone-Receptor Positive, Human Epidermal Growth Factor Receptor 2-negative Breast Cancer

Description:

This PQI will outline the applicability, process, and importance of ESR1 mutation testing in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+HER2-) metastatic breast cancer.

Background:

ESR1 mutations act as critical drivers of endocrine resistance in breast cancer 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.[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 and NCCN Guidelines recommend testing for these mutations at each point of metastatic progression to inform treatment decisions.[6,7]

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.[8,9] 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 (NGS or ddPCR) that claim ESR1 mutation coverage.[10] If considering initiation of elacestrant for a patient testing positive for ESR1 mutation, care teams should consult diagnostic manufacturers' technical information to verify that their chosen test covers the same ESR1 mutations as those in the EMERALD clinical trial.[11] 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 as it is an acquired mutation.[7]

PQI Process:

Patient ESR1 mutation testing eligibility:

- First line metastatic HR+HER2- disease: particularly if patient has a history of recent exposure to endocrine therapy (ET) (e.g. in the adjuvant setting)
    - Consider blood based ctDNA testing for ESR1 mutation (e.g. Guardant360 CDx)
- Second line metastatic HR+HER2- disease: progressing on aromatase inhibitor or fulvestrant-based ET
    - Highly recommend blood based ctDNA testing for ESR1 mutation (e.g. Guardant360 CDx)
- Third line metastatic HR+HER2- disease and beyond which has remained ESR1 wild type on previous testing: the decision to test for ESR1 mutation may be influenced by endocrine sensitivity of disease
    - Consider blood based ctDNA testing for ESR1 mutation (e.g. Guardant360 CDx)
- ESR1 mutation testing preformed on blood or tissue obtained *at the time of progression* is essential as ESR1 mutations most commonly present in response to selection pressure following endocrine-based therapy[6]
- Liquid-biopsy based ctDNA testing is generally considered more sensitive for ESR1 mutation detection vs tissue biopsy[6]

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Patient-Centered Activities:

- Blood-based testing is non-invasive and generally considered minimal risk
- Treatment options for patients with history of ET (with or without CDK4/6 inhibitor treatment) and a detectable ESR1 mutation include[6]:
  - Elacestrant
  - Other ET either alone or in combination with targeted agents such as alpelisib (for PIK3CA-mutated tumors) or everolimus
- Patient assistance resources to help with costs associated with mutation testing
  - Patient Advocate Foundation's Personalized Medicine CareLine
  - Patient Advocate Foundation's Co-Pay Relief Program for Cancer Genetic and Genomic Testing
  - Guardant Access

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