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Real-World *ESR1* Mutation (*ESR1*m) Testing and Positivity Rates in Patients With ER+, HER2- Metastatic Breast Cancer (MBC)

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OBJECTIVE

We estimated real-world rates of *ESR1* testing and mutation positivity in patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC) from the Flatiron Health Research Panoramic dataset to identify testing patterns and support optimization of *ESR1* testing in the real world

CONCLUSIONS

- Among real-world patients with ER+, HER2- MBC, 49% had ≥1 *ESR1* test during the full testing period
- At first-line (1L) initiation, the *ESR1* mutation (*ESR1*m)-positive rate was 25% among tested patients with endocrine-resistant MBC
- At second-line (2L) initiation, the *ESR1*m-positive rate was 32-34% among tested patients with endocrine-resistant or endocrine-sensitive MBC
- During 1L, ~60% of tested patients had *ESR1* tests in tissue and ~40% in blood
- Lower rates of *ESR1*m positivity were observed in the real world compared with those in clinical trials[2-4]
  - Potentially due to frequent use of tissue-based testing, which is less sensitive than recommended blood-based circulating tumor DNA (ctDNA) testing[1]
- **These results highlight the need for increased awareness of *ESR1* testing using blood-based ctDNA at the guideline-recommended time points of disease recurrence and each progression event after prior endocrine therapy (ET) in patients with MBC[1] to optimize patient identification for targeted therapies in ER+, HER2- MBC**

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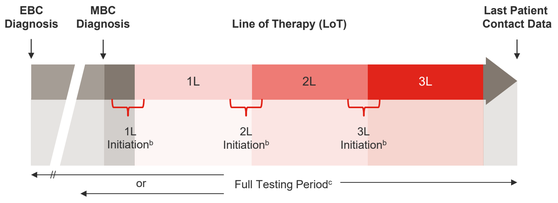
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BACKGROUND

- As the MBC treatment landscape rapidly evolves, understanding *ESR1* testing patterns and *ESR1*m positivity rates in patients with ER+, HER2- MBC is essential to identify patients who may benefit from targeted therapies
- Existing guidelines recommend routine testing for emergence of *ESR1*m at recurrence or progression on ET in patients diagnosed with ER+, HER2- MBC[1]
  - Blood-based testing is recommended over tissue-based testing as it has increased sensitivity of *ESR1*m detection[1]
- Real-world data on *ESR1* testing and mutation rates are limited

METHODS STUDY SCHEMA

ESR1 Testing Window Definitions Using the Flatiron Health Research Panoramic Database[a]



Patient Population
- Diagnosed with ER+, HER2- MBC from January 1, 2020 to March 31, 2025; could have had an EBC diagnosis from January 1, 2011 to March 31, 2025
- Age ≥18 years at diagnosis
- Initiated 1L therapy with aromatase inhibitor (AI) OR selective estrogen receptor degrader (SERD) ± CDK4/6 inhibitor (CDK4/6i) from January 1, 2020 to December 31, 2024

Endocrine Resistant
- Evidence of EBC diagnosis in the database
- Developed MBC while on or ≤12 months after completing adjuvant AI ± CDK4/6i

Endocrine Sensitive
- No evidence of EBC diagnosis or adjuvant therapy in the database; majority likely de novo MBC
- Initiated AI ± CDK4/6i in 1L

[a]The Flatiron Health Research Database is a de-identified, US-based electronic health record database; [b]LoT initiation window went from 90 days before to 28 days after LoT initiation date; [c]Full testing period: From EBC diagnosis or 90 days prior to MBC diagnosis (if no evidence of EBC diagnosis) to last patient contact data.

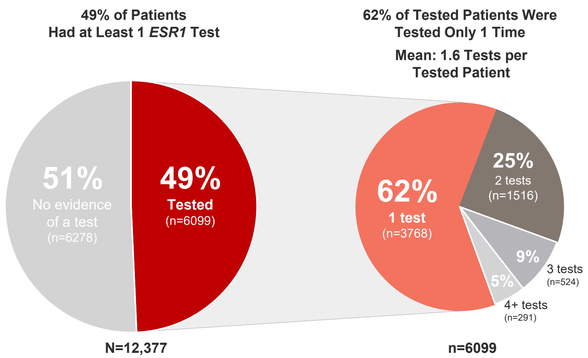
RESULTS

Patient Demographics and Clinical Characteristics

Characteristic	Overall[a] (N=12,377)	Endocrine Resistant (n=2152)	Endocrine Sensitive (n=5772)
Age, mean (SD), years	66 (13)	67 (11)	67 (13)
Female	12,225 (98.8)	2134 (99.2)	5713 (99.0)
Race/ethnicity			
White	7315 (59.1)	1336 (62.1)	3280 (56.8)
Black or African American	1271 (10.3)	240 (11.2)	594 (10.3)
Hispanic or Latino	866 (7.0)	167 (7.8)	373 (6.5)
Asian	275 (2.2)	48 (2.2)	134 (2.3)
Other	865 (7.0)	175 (8.1)	329 (5.7)
Unknown/not documented	1785 (14.4)	186 (8.6)	1062 (18.4)
Socioeconomic status (quintile)			
1 - low	1883 (16.7)	308 (15.7)	917 (17.4)
2	2190 (19.4)	363 (18.5)	1052 (20.0)
3	2434 (21.5)	434 (22.1)	1140 (21.7)
4	2612 (23.1)	466 (23.8)	1176 (22.3)
5 - high	2186 (19.3)	389 (19.8)	980 (18.6)
Missing	1072	192	507
ECOG PS at MBC diagnosis			
0	4730 (44.2)	892 (46.5)	1983 (40.3)
1	3876 (36.2)	722 (37.6)	1766 (35.9)
2	1457 (13.6)	221 (11.5)	788 (16.0)
≥3	632 (5.9)	84 (4.4)	381 (7.7)
Missing	1682	233	854

[a]There were 4,453 patients who met overall study inclusion criteria but did not meet subgroup definitions for endocrine resistant or endocrine sensitive MBC in this study.
Note: Data are n (%) unless otherwise indicated.

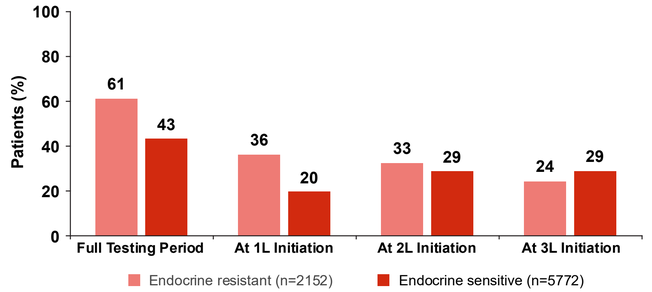
Overall, 49% of Patients Had at Least 1 *ESR1* Test Any Time During the Full Testing Period



Note: Full testing period: From EBC diagnosis or 90 days prior to MBC diagnosis (if no evidence of EBC diagnosis) to last patient contact data.

ESR1 Testing Rates at LoT Initiation

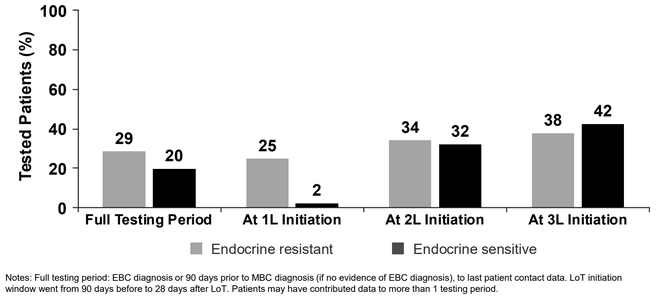
- **At each LoT initiation, between 20-36% of patients received an *ESR1* test**



Notes: Full testing period: EBC diagnosis or 90 days prior to MBC diagnosis (if no evidence of EBC diagnosis), to last patient contact data. LoT initiation window went from 90 days before to 28 days after LoT initiation date. Patients may have contributed data to more than 1 testing period.

*ESR1*m Positivity Rates at LoT Initiation

- *ESR1*m positivity rate increased with each LoT
- At 1L initiation, the endocrine-resistant MBC *ESR1*m-positive rate was 25% among tested patients
- At 2L initiation, the *ESR1*m-positive rate was 32-34% among tested patients

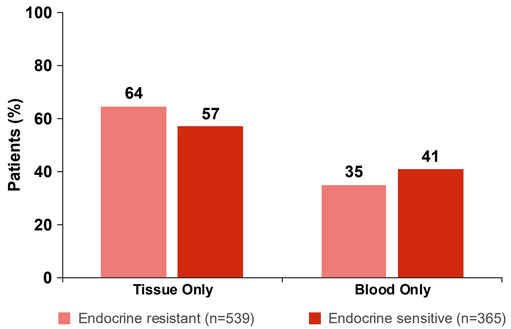


Notes: Full testing period: EBC diagnosis or 90 days prior to MBC diagnosis (if no evidence of EBC diagnosis), to last patient contact data. LoT initiation window went from 90 days before to 28 days after LoT. Patients may have contributed data to more than 1 testing period.

Exploratory Analysis by *ESR1* Test Sample Type in the Flatiron Health Research Database:[a] *Based on Initial ESR1 Test During 1L*

ESR1 Test Sample Types

- During 1L,[b] ~60% of patients had their initial *ESR1* test in tissue only and ~40% were in blood only[c]



[a]Flatiron Health Research data from a subset of patients (n=2028) with information on test sample type. [b]During 1L was from start date to end date of 1L + 28 days for patients in the Flatiron Health Research Database subset who were diagnosed with MBC from January 1, 2019 - October 31, 2024, and initiated a 1L therapy between January 1, 2019 - July 31, 2024.
[b]Both tissue and blood <1%; Other/unknown <1%.

LIMITATIONS

- Progression events were not available in this dataset; therefore, switching LoT was used to anchor the testing windows
- Within the endocrine-sensitive group, patients may have had an EBC diagnosis/adjuvant therapy that preceded the database start date or occurred outside the Flatiron Health network and was not captured in this study
- Patients could have had *ESR1* testing outside the Flatiron Health network that was not captured in these data
- Sample type was unavailable in the Panoramic dataset

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1. Burstein HJ, et al. *J Clin Oncol.* 2023;41:3423-3425. 2. Jhaveri KL, et al. *N Engl J Med.* 2025;392:1189-1202. 3. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256. 4. Campone M, et al. *N Engl J Med.* 2025;393:556-568.

Abbreviations: *1L, first-line; 2L, second-line; 3L, third-line; AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; EBC, early breast cancer; ECOG, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor-positive; ESR1m, ESR1 mutation; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-negative; LoT, line of therapy; MBC, metastatic breast cancer; SD, standard deviation, SERD, selective estrogen receptor degrader*

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