



## *BRCA1/2* mutation prevalence among triple-negative breast cancer patients from a large commercial testing cohort\*

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### Background:

*BRCA1/2* mutation identification among triple-negative breast cancer (TNBC) patients has gained importance due to multiple studies demonstrating the high likelihood of mutations in this population.<sup>1,5</sup> Mutation identification has important cancer-risk management implications for patients and their relatives, and mutation status has gained importance in guiding patient selection for studies involving PARP inhibitors that target underlying defects in DNA repair.<sup>7</sup> Initial studies evaluating the prevalence of *BRCA1/2* mutations in TNBC patients were carried out in small cohorts of selected patients with a high prior probability of a *BRCA1/2* mutation based on ethnicity (Ashkenazi Jewish ancestry), young age at diagnosis, and/or significant family history.<sup>3,4,5</sup> In these studies, mutation prevalence ranged from 11% - 39%, however not all studies included full analysis of both *BRCA1* and *BRCA2*. Recently, two studies were published that looked at *BRCA1/2* mutation prevalence in unselected cohorts of TNBC patients, and found mutation prevalence ranged from 10.6% - 18.2%.<sup>1,2</sup> In 2011 the National Comprehensive Cancer Network (NCCN) added a recommendation for *BRCA1/2* testing for TNBC patients diagnosed at age  $\leq 60$ .<sup>6</sup> The current study was undertaken to look at *BRCA1/2* mutation prevalence for TNBC patients undergoing commercial testing for *BRCA1/2*.

### Methods:

- Following the NCCN 2011 Hereditary Breast and Ovarian Cancer (HBOC) Testing Criteria update, data from serial cohorts of > 5,000 Ashkenazi Jewish and > 65,000 non-Ashkenazi Jewish breast cancer patients undergoing commercial *BRCA1/2* testing were analyzed to evaluate mutation prevalence in correlation with triple negative receptor status.
  - Age at diagnosis, ethnicity, and provider-reported triple negative receptor status were obtained from test requisition forms completed by ordering providers, and correlated with test results.
  - Non-Ashkenazi Jewish patients typically received full *BRCA1/2* sequencing with or without comprehensive large rearrangement analysis, while most Ashkenazi Jewish patients were tested for 3 founder mutations, with some patients having full sequencing and comprehensive large rearrangement analysis.
  - Data for patients of African and Ashkenazi Jewish ancestry were specifically evaluated due to the higher rates of TNBC in patients of African ancestry, and higher rates of *BRCA1/2* mutations in the Ashkenazi Jewish population.
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## Results:

- In the testing cohort of >65,000 breast cancer patients, 9.7% of patients had a TNBC. Figure 1 illustrates that this percentage was higher for patients of African ancestry (16.5%), and lower for Ashkenazi Jewish ancestry (4.5%). Figure 2 shows the *BRCA1/2* mutation rates for TNBC patients for all ancestries (11.4%), Ashkenazi Jewish ancestry (19.9%), and African ancestry (12.0%).
- Table 1 lists *BRCA1/2* mutation rates by age, and this is presented graphically in Figure 3. For the TNBC population undergoing *BRCA1/2* testing, 9.1% of patients were diagnosed after age 60 with a mutation positive rate of 7.4% in this group (Table 2). Of those diagnosed at age 60 or younger, the mutation positive rate was 11.7%. For all ancestries, the mutation rate did not drop below 5% until after age 70.

Figure 1: Percentage of testing population with TNBC in a cohort of >65,000 patients.

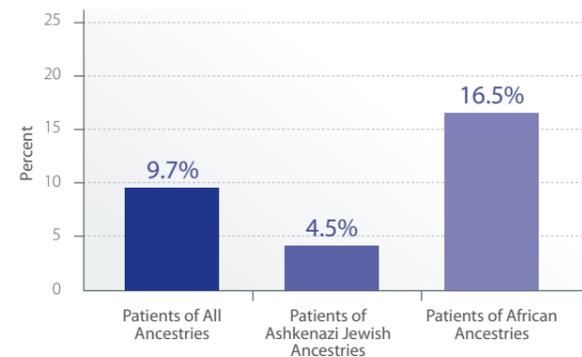


Figure 2: *BRCA1/2* mutation rates for all TNBC patients, and subsets of Ashkenazi Jewish and African ancestries.

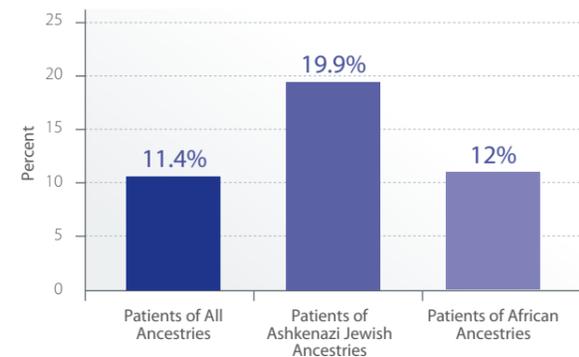
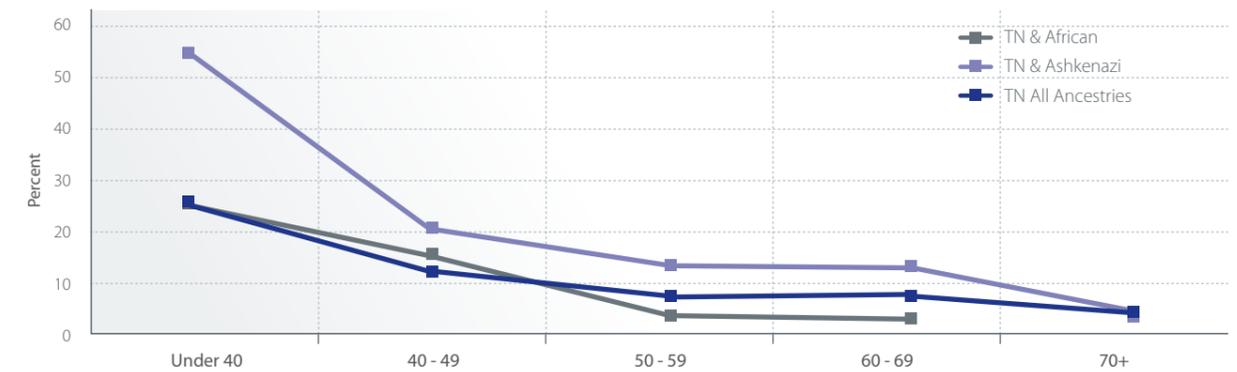


Table 1: *BRCA1/2* mutation rates for TNBC patients by age and selected ancestry.

Age Range	All Ancestries (% Positive)	Ashkenazi Jewish (% Positive)	African (% Positive)
Under 40	23.00%	55.20%	22.80%
40 - 49	11.50%	21.10%	13.20%
50 - 59	7.10%	13.00%	5.80%
60 - 69	7.90%	12.00%	2.50%
70+	4.90%	4.30%	---
All*	11.40%	19.90%	12.00%

\*Includes patients with age not provided  
 --- Indicates n ≤ 20 patients

Figure 3: *BRCA1/2* mutation rates for TNBC patients by age and selected ancestries.



## Discussion:

This analysis of >6,500 TNBC patients provides the most robust estimate to date of *BRCA1/2* mutation prevalence among TNBC patients of all ages. Current guidelines support *BRCA1/2* testing for TNBC patients diagnosed at age ≤60.<sup>6</sup> This study found a *BRCA1/2* mutation rate of nearly 12% in this population, confirming the importance of offering testing to TNBC patients diagnosed at age 60 or younger, regardless of ancestry or additional personal or family history.

For TNBC patients diagnosed after age 60, this study found a *BRCA1/2* mutation rate of 7.4%, which confirms the importance of evaluating TNBC patients diagnosed at any age to determine appropriateness for *BRCA1/2* testing. In this study, it is likely that TNBC patients diagnosed after age 60 met testing criteria based on additional personal and/or family history.

In considering selected ancestries, this study found a higher *BRCA1/2* mutation rate overall for patients of Ashkenazi Jewish ancestry having TNBC, as expected based on the high carrier frequency in this population in general.

Only a small percent of Ashkenazi Jewish patients undergoing testing had TNBC, however it is possible that TN status is underreported by ordering providers, as these patients meet criteria for testing regardless of receptor status. In contrast, the testing population of African ancestry had the highest rate of TNBC reported, and in these patients the *BRCA1/2* mutation rate was similar to patients of all ancestries.

Nearly 10% of the *BRCA1/2* testing population had TNBC, which is lower than the historical rate of 15 - 20% of breast cancers being TN. However, it is anticipated that the rate of TNBC overall may decrease due to stricter criterion for TNBC that was recently implemented.<sup>8</sup> Given the high rate of *BRCA1/2* mutations in the TNBC population in prior studies<sup>1-5</sup> and confirmed by the current study, this data suggests the need for improvement in identification of TNBC patients as *BRCA1/2* testing candidates, as they may be underrepresented in the testing population.

Table 2: *BRCA1/2* mutation rates among TNBC patients by ethnicity and age.

Ethnicity	Mutation Rates Among TNBC Patients	
	Age ≤ 60	Age > 60
All Ancestries	11.7%	7.4%
Ashkenazi Jewish	23.9%	8.7%
African	12.4%	2.7%

## Limitations:

- The testing population studied here is representative of a selected population with the majority of patients undergoing testing due to meeting societal guideline and payor criteria.
- This data was obtained from health care provider report of cancer diagnosis and triple negative status.

## Summary:

- This study provides the most robust estimate to date of BRCA1/2 mutation prevalence among TNBC patients of all ages, and confirms a high mutation rate in this population (11.4%).
- In accordance with multiple professional society guidelines, all breast cancer patients should be evaluated for indicators of a hereditary breast cancer syndrome. For patients not meeting simple criteria based on their own diagnosis, it is important to look for additional criteria that may indicate testing (TN status, Ashkenazi Jewish ancestry, additional personal and/or family history).
- For TNBC patients diagnosed after age 60, the mutation rate seen among these patients (7.4%) illustrates the importance of looking for additional personal and/or family history to assess appropriateness for testing in this group.
- Genotype information from both tumor and germline analysis is increasingly becoming standard of care as a tool to guide therapy in patients with multiple tumor types. It is important that guidelines regarding patient criteria for genetic testing keep pace with emerging data to enable access to genetic tests for all appropriate patients.

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