Usefulness of Retrospective Analysis of BART Eligibility

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Abstract: In 2006 Myriad Genetic Laboratories, Inc. introduced BRACAnalysis Large Rearrangement Test (BART) to detect additional large genomic rearrangements in BRCA1 and BRCA2, which went undetected by Comprehensive BRACAnalysis. We retrospectively identified all patients within our community oncology practice that underwent Comprehensive BRACAnalysis testing from 2002 through 2006 and evaluated each of the 37 negative patients for BART eligibility to identify potential candidates for the additional testing. Two patients met published criteria, of which one was deceased and the other is considering BART testing. Overall, retrospective systematic review to identify patients eligible to undergo BART testing who have previously tested negative by BRACAnalysis will have a very low yield. We recommend patients with prior negative Comprehensive BRACAnalysis be evaluated for BART eligibility as they are seen in clinic for follow-up and offered the additional testing at that time if clinically appropriate.

Keywords: Breast cancer, Genetic testing, BRCA, BART.

INTRODUCTION

Genetic testing for deleterious BRCA1 and BRCA2 mutations was introduced in the mid-1990s. Germline mutations in these genes are known to be the underlying basis of hereditary breast and ovarian cancer syndromes, portending to their carriers a higher lifetime risk of these cancers. Since that time, a generation of cancer patients have had the opportunity to clarify the risk for themselves and their family members of developing breast, ovarian and other cancers.

In 2006 Myriad Genetic Laboratories, Inc. introduced BRACAnalysis Large Rearrangement Test (BART) to detect additional large genomic rearrangements for both BRCA1 and BRCA2 that were undetected by the previous methodology. Comprehensive BRACAnalysis testing (the preceding method offered for the detection of BRCA1 and BRCA2 mutations) consists of complete sequencing of the BRCA1 and BRCA2 genes as well as testing for 5 common point mutations in BRCA1. The supplementary BART testing detects additional deleterious large DNA rearrangements in BRCA1 and BRCA2 using techniques such as quantitative endpoint polymerase chain reaction; this methodology can detect mutations that are present with less frequency, in theory providing a higher likelihood of detecting a deleterious mutation if present [1].

Since its introduction, BART has been done automatically in very high-risk patients who have a negative result on Comprehensive BRACAnalysis testing in order to identify additional patients with increased risk of breast and ovarian cancer. The automatic performing of BART testing (without the placement of an additional request or requiring any additional cost) in the setting of negative Comprehensive BRACAnalysis testing will be referred to as “reflex testing.”

To be considered very high-risk for genetic mutations in BRCA1 and BRCA2 patients must be:

1) diagnosed with breast cancer before the age of fifty, ovarian cancer at any age, male breast cancer at any age, and either
   a. have two first or second-degree female relatives with either breast cancer before the age of fifty and/or ovarian cancer at any age and/or male breast cancer at any age, or
   b. any patient who has had breast cancer before the age of fifty and ovarian cancer at any age.
2) any patient who has had breast cancer after the age of fifty and ovarian cancer at any age with one additional qualifying diagnosis of breast or ovarian cancer in a first or second-degree relative [2].

Within this very high-risk population of patients the probability of having a mutation in BRCA1 or BRCA2 is considered to be >30%. The addition of BART to Comprehensive BRACAnalysis increases the overall detection rate of BRCA1 and BRCA2 mutations by an additional 3% [3].

This study was designed to evaluate the patients in a community oncology practice who were tested for genetic mutations in the BRCA1 and BRCA2 genes prior to 2006 and to identify those very high-risk patients who, if they were tested today, would qualify for reflex BART. Secondly, the at-risk patients were contacted to make them aware of the availability of BART and offer them the opportunity to undergo the additional testing. In doing so, we evaluated the yield and utility of performing a retrospective analysis in a community based oncology practice setting of negative
Comprehensive BRACAnalysis tests to determine eligibility for BART, offering the additional testing to those eligible.

**METHODS**

We retrospectively identified all patients within our community oncology practice that underwent Comprehensive BRACAnalysis testing from 2002 through 2006. In order to ensure all patients were captured in our analysis we performed a chart review of the charts kept by our breast cancer coordinator and requested patient lists from Myriad Genetic Laboratories, Inc. containing information about patient test results for each of our oncologists during our target years. Patient demographic data was extracted from each of the patient charts, including a detailed personal and family history of breast and ovarian cancer.

Eligibility for BART was determined using the criteria developed by Myriad Genetic Laboratories, Inc. which is currently being utilized to qualify patients for reflex BART if Comprehensive BRACAnalysis is negative.

**RESULTS**

A total of 113 patients were identified that were evaluated for genetic testing for BRCA1 and BRCA2 mutations from 2002 through 2006. Of those patients, 56 had the diagnosis of cancer and 42 were ultimately tested. Five patients had initial positive results. Of the remaining 37 patients, two met the criteria for reflex BART testing. One of the two patients was deceased at the time of the chart review; the other had moved out of the area and is currently under the care of a new oncologist.

Of the 35 patients who did not meet criteria for BART testing 26 did not have a sufficient family history to be considered very high-risk, two were over the age of 50 at the time of diagnosis and did not have ovarian cancer and seven patients failed to meet eligibility criteria for both age and family history (Table 1).

Table 1. Cause of Ineligibility for BART Testing

<table>
<thead>
<tr>
<th>Criteria for BART Testing Not Satisfied</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td>26</td>
</tr>
<tr>
<td>Age at Diagnosis &gt;50 years old without ovarian cancer</td>
<td>2</td>
</tr>
<tr>
<td>Family History and Age</td>
<td>7</td>
</tr>
<tr>
<td>Already Positive by Comprehensive BRACAnalysis</td>
<td>5</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Improvements and alterations in genetic testing technologies have the potential to identify patients at increased risk who have previously eluded detection, thereby possibly clarifying risk of disease and changing treatment decisions. It is therefore reasonable to consider applying new testing modalities to previously screened patients who have tested negative.

Our retrospective evaluation of patients who previously tested negative for BRCA1 and BRCA2 mutations but would currently qualify for reflex BART testing yielded only 2 patients of 37 with negative screening for genetic mutations. Of the two eligible patients, one was a male who initially presented with metastatic disease and had succumbed to his disease prior to the time of the chart review. The second patient had moved out of the area, was cancer free and under the care of a new oncologist with whom she intends to discuss BART testing.

We found that 5.4% of our patients who had negative Comprehensive BRACAnalysis prior to the availability of BART testing were considered very high-risk according to the criteria set forward by Myraid Laboratories, Inc. With an estimated increase in overall BRCA1 and BRCA2 mutation detection rate of 3%, 617 patients with prior negative Comprehensive BRACAnalysis testing would need to be evaluated, identifying 33 very high-risk patients to undergo BART testing in order to detect one additional BRCA1 or BRCA2 mutation.

Currently, reflex BART testing is included within the cost of Comprehensive BRACAnalysis; however, if BART is ordered alone, as would be the case in a very high-risk patient with a negative BRACAnalysis prior to the availability of BART, the cost of the test is $650. Therefore, $21,450 would need to be spent to perform the BART testing necessary to detect one additional BRCA mutation. In addition to the economic aspect, considerations should be made to address the equally important emotional and psychological aspects of this endeavor, as offering the additional testing to patients who were formerly declared to be free of genetic mutations had the potential to renew anxiety that had been previously laid to rest.

Additionally, the percentage of genetic mutations that are detected by BRACAnalysis and BART testing vary significantly by ancestry. The prevalence of mutations detected by BART is much higher in patients of Latin American/Caribbean and Neareast/Mideast ancestry as opposed to patients with Western/Northern European ancestry. Both of the patients we identified in our practice had Western/Northern European ancestry. The prevalence of mutations detected by BART is much higher in patients of Latin American/Caribbean and Neareast/Mideast ancestry as opposed to patients with Western/Northern European ancestry. Both of the patients we identified in our practice that would have been eligible for BART testing were of Western/Northern European ancestry, therefore falling into the latter group who are less likely to have a mutation detected by BART testing. This discrepancy in prevalence should be taken into consideration when selecting patients to send for BART testing in the setting of a historically negative BRACAnalysis testing [4].

In conclusion, retrospective systematic review of patients who tested negative by Comprehensive BRACAnalysis prior to the availability of BART to identify very high-risk patients who should undergo BART testing will have a very low yield. It is our recommendation that patients with prior negative Comprehensive BRACAnalysis should be evaluated for BART eligibility as they are seen in clinic for follow-up and offered the additional testing at that time, if clinically appropriate.

**ACKNOWLEDGEMENT**

Declared none.

**CONFLICT OF INTEREST**

Declared none.
REFERENCES


