CLINICAL SUMMARY

Testing for Hereditary Breast and Ovarian Cancer Syndrome

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For patients meeting testing criteria for HBOC, "Comprehensive genetic testing includes full sequencing of *BRCA1/BRCA2* and detection of large genomic rearrangements".

(NCCN Guidelines Version 1.2012 Hereditary Breast and/or Ovarian Cancer Syndrome HBOC-2).

Testing for large genomic rearrangements is referred to as **BART**™ (**B**RAC***Analysis***®** **R**earrangement **T**est).

1. For specific details of the criteria, see https://www.myriadpro.com/BRAC_BART
2. www.nccn.org

Large Rearrangements in *BRCA1* and *BRCA2*: Clinical Significance, Prevalence, and Testing Strategy

The majority of *BRCA1* and *BRCA2* mutations consist of small changes in the DNA sequence that have significant impact on protein function and therefore on the risk for cancer. Historically, testing for *BRCA1* and *BRCA2* has included sequencing of both genes and evaluation of five common large rearrangements (5-site large rearrangement panel). In 2006, testing for additional large rearrangements (BART™) was introduced and became a routine part of *BRCA1* and *BRCA2* testing for high-risk[1] patients and an option for all other patients. The authors of this paper examined the contribution of large rearrangements across different risk groups and ethnicities. Recognition of the relative importance of large rearrangements is reflected in the 2012 update to the National Comprehensive Cancer Network (NCCN) Guidelines recommending large rearrangement testing as a routine component of testing for **all** patients for whom testing for *BRCA1* and *BRCA2* is appropriate.

Judkins T, et al. Clinical Significance of Large Rearrangements in *BRCA1* and *BRCA2*. *Cancer* 2012 (Epub ahead of print).

Purpose:

To characterize the mutation profile of *BRCA1* and *BRCA2*, stratified by mutation type (detected by sequencing vs large rearrangement), prior risk, and patient ancestry in a diverse group of patients more representative of the US population.

Design and Methods:

Data from two groups of patients referred for clinical analysis of *BRCA1/2* between July 2007 and April 2011 were reviewed. The "high-risk" group was defined as those meeting clinical criteria predicting relatively high probability of a *BRCA1/2* mutation.[1] The "elective" group consisted of patients who did not meet the high-risk criteria, but for whom BART was ordered as an elective reflex test.

Proportion of Mutations Detected by Sequencing vs Large Rearrangement Testing (LR)

	Sample Size	Overall Mutation Rate	Sequencing Mutation Rate	LR Mutation Rate*	LR % of Overall Mutations*
High-Risk	25,535	23.8%	21.5%	2.4%	9.9%
Elective	22,921	8.2%	7.8%	0.5%	5.9%

*Approximately 3 in 4 large rearrangements (LR) would only have been detected by BART

Results:

- A significant proportion of all mutations identified were large rearrangements
- Large rearrangements were more common among, but not limited to, persons with a strong personal and family history of breast and ovarian cancer (10% vs 6%)
- Large rearrangements were more common among individuals of Latin American/Caribbean ancestry (21% in the high-risk group and 16% in the elective group)
- The 5-site large rearrangement panel found about one third of the large rearrangements among Northern Europeans, but almost none among patients of any other ethnicity

Bottom Line:

Large rearrangements in *BRCA1* and *BRCA2* are a significant contribution to hereditary breast and ovarian cancer (HBOC), particularly in certain ethnic groups, therefore making it appropriate to include BART as part of routine testing for *BRCA1* and *BRCA2*. The NCCN updated their guidelines for HBOC risk assessment for 2012 to reflect this important finding.[2]

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