



Large Genomic Rearrangements in *BRCA1* and *BRCA2*: Implications for Patient Care

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Hereditary breast cancer is responsible for about 5%–10% of all breast cancer cases and is frequently associated with the inheritance of a germline mutation in one of two genes, *BRCA1* (chromosome 17) or *BRCA2* (chromosome 13). Inheritance of a mutation in one of these genes confers a high cumulative risk of breast (90% lifetime risk) or ovarian (44% lifetime risk) cancer (Daly et al., 2013). To date, *BRCA1* and *BRCA2* genetic testing only is available through one company, Myriad Genetics Laboratories (MGL), as a result of patent issues surrounding these two genes. In 1996, MGL introduced Comprehensive BRACAnalysis[®], which included the sequencing of *BRCA1* and *BRCA2*. Because of technological advancement, MGL added a five-site rearrangement panel to Comprehensive BRACAnalysis in 2002 to detect five recurring large genomic rearrangements (LGR) in *BRCA1*. Additional technological advances led to the addition in 2006 of the BRACAnalysis Large Rearrangement Test (BART) as a separate but full LGR test for *BRCA1* and *BRCA2*. The Comprehensive BRACAnalysis and BART tests were ordered as two distinct tests. In October 2012, Medicare approved BART as a reimbursable test, provided specific guidelines were met, based on the 2013 National Comprehensive Cancer Network guideline (Daly et al., 2013) recommending LGR testing for all patients undergoing testing for *BRCA1* and *BRCA2*. Beginning in January 2013, MGL began incorporating BART testing into routine *BRCA1* and *BRCA2* testing, now termed Integrated BRACAnalysis (MGL, 2012).

Laboratory Technology

Until the addition of BART, *BRCA1* and *BRCA2* testing focused on the

identification of point mutations (small deletions and insertions) that resulted in (a) protein truncation, (b) disruption of messenger RNA processing, or (c) amino acid substitutions that had a significant negative impact on protein function. This alteration in protein function results in altered cell function and, ultimately, malignancy. The small mutations are typically detected by Sanger DNA sequencing of polymerase chain reaction (PCR)-amplified gene segments (Judkins et al., 2012). Comprehensive BRACAnalysis testing uses PCR-based bidirectional Sanger sequencing of both *BRCA1* and *BRCA2*. This includes the analysis of about 5,400 base pairs, including 22 coding exons and 750 introns, in *BRCA1* and about 10,200 base pairs, including 26 coding exons and 900 introns, in *BRCA2* (Judkins et al., 2012). BART testing uses technology to detect another mechanism of gene inactivation resulting from the rearrangement of large tracts of genomic DNA.

Many of the deleterious mutations caused by LGRs were missed when the testing was restricted to PCR-based testing alone, which is incapable of detecting LGRs (Sluiter & Rensburg, 2011). Multiplex ligation-dependent probe amplification (MLPA) is the most commonly used technique to detect LGRs. MLPA is highly sensitive and relatively inexpensive compared to other genetic testing methods (Rodríguez, Torres, Borràs, Salvat, & Gumà, 2010).

Pathophysiology

Arthrobacter luteus (*Alu*) restriction endonuclease element is a short stretch of repetitive DNA. The human genome contains about one million copies of interspersed *Alu* that are thought to mediate chromosomal rearrangements

resulting in translocations, duplications, inversions, or deletions (Ewald et al., 2009). *BRCA1* is rich in *Alu* sequences that are associated with LGRs (Hansen et al., 2009; Machado et al., 2007; Stadler et al., 2010). To date, at least 81 different LGRs have been found in the *BRCA1* gene. *Alu* sequences are much less common in *BRCA2*, which might provide insight as to why fewer LGRs are associated with the *BRCA2* gene (Sluiter & Rensburg, 2011; Stadler et al., 2010). LGRs in *BRCA1* account for an estimated 8%–27% of all *BRCA1* mutations (Sluiter & Rensburg, 2011; Stadler et al., 2010). LGRs are less common in the *BRCA2* gene and account for 0%–11% of all *BRCA2* mutations (Stadler et al., 2010).

Ethnic Clinical History Indicators

The founder mutations, 187delAG *BRCA1*, 5385insC *BRCA1*, and 6174delT *BRCA2* in people of Ashkenazi or Eastern European Jewish ancestry account for 90% of all deleterious mutations in this population (Weitzel et al., 2012). These typically are detected with the Multisite 3 BRACAnalysis. LGRs are uncommon in people of Ashkenazi Jewish background (Palma et al., 2008; Stadler et al., 2010).

African and Latin American or Caribbean ancestry has been associated with a higher incidence of LGRs and may be related to a founder effect (Judkins et al., 2012). In particular, one LGR, *BRCA1* ex9-12del, is considered a Mexican founder mutation and may eventually lead to a targeted panel for testing in that ethnic group similar to the Multisite 3 BRACAnalysis. Risk for LGRs also may be higher in those of Danish ancestry and Spanish ancestry (Hansen et al., 2009; Valle et al., 2010).