



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

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG

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).

Implications for Nurses

The usefulness of *BRCA1* and *BRCA2* genetic testing in the area of prevention and early detection should not be underestimated. Effective risk reduction procedures exist, including prophylactic oophorectomy or mastectomy, chemoprevention, and screening measures, such as breast magnetic resonance imaging. When an appropriate comprehensive prevention and risk reduction plan is incorporated into the care of an individual at high risk for breast cancer, morbidity and mortality associated with breast cancer is decreased (Lindor, McMaster, Lindor, & Greene, 2008). This underscores the need for accurate and comprehensive detection of all mutations. Unfortunately, current criteria and risk models do not always correctly categorize those who might be at risk for having a deleterious germline mutation (Kwon et al., 2010). In addition, family history information changes and evolves over time. A patient may initially present with a history that does not meet the criteria for genetic testing, but if the personal or family history changes (maternal or paternal), the patient may become eligible for genetic testing of *BRCA1* and *BRCA2*, or be considered for testing of mutations on other less common genes (e.g., *CHEK2*, *TP53*). Updates in genetic testing technology, such as what occurred with LGRs, also necessitate the need to re-evaluate if a patient or family might benefit from additional genetic testing.

When BART was initially introduced, MGL established very specific testing criteria based on personal and family history that selected individuals with a greater than 30% risk of carrying a mutation in *BRCA1* or *BRCA2* (Qureshi et al., 2009). When the sample was submitted, if an individual met these criteria, BART was performed along with Comprehensive BRACAnalysis. If the individual did not meet these criteria, only the Comprehensive BRACAnalysis was performed. The individual had the option of adding BART for an additional cost (about \$700), which was not consistently covered by insurance. Some providers and institutions routinely offered BART testing; others did not. Initially, the uptake of this technology was low (Shannon et al., 2011). Consequently, many women have had Comprehensive BRACAnalysis but have not had BART testing; some

of these individuals may have a LGR that has not been identified (Hartman et al., 2012; Shannon et al., 2011). Just as updating the family history of patients on at least an annual basis is important, healthcare providers should re-evaluate patients to determine if additional genetic testing might be indicated. Nurses should ascertain whether patients have had the opportunity to have the most comprehensive genetic testing available (Rubinstein, 2008).

Ordering a genetic test is different from ordering other laboratory tests. A genetic test typically is preceded by counseling that includes a discussion of benefits, risks, limitations, possible outcomes of testing, and management strategies, depending on test results. A major limitation of genetic testing is that not all mutations are detectable with current technology. Most genetics professionals will recommend that patients who have substantial family history and have tested negative for known mutations recontact the genetics professional every 12–18 months to determine if technologies have been updated or if new genetic testing options are available (Mahon, 2012). Patients also may be recommended to pursue preventive or risk-reduction interventions consistent with a high risk, even if that risk has not been confirmed by genetic testing. Given the explosion of genetic knowledge, a genetics professional cannot be expected to re-contact every patient when a change occurs in available technology (Pyeritz, 2011). For this reason, oncology nurses need to be aware of the testing patients have received, as well as the technological changes in genetic testing. Patients who have tested negative in the past should be educated that a new technology or testing may be available and that individual should be referred to a genetics professional. Nurses need to be able to examine a patient's test report and determine if the testing has been completed. If the report does not state comprehensive rearrangement analysis under both *BRCA1* and *BRCA2*, the testing might not be complete and additional education and a referral for additional testing are indicated. The date of the test also will assist in identifying which panel a patient may have received based on the technology available at that time. Viewing the actual test result is best, so nurses should instruct the patient to bring a copy to the genetics professional.

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG, is a professor of internal medicine and adult nursing in the School of Nursing at Saint Louis University in Missouri. No financial relationships to disclose. Mahon can be reached at mahonsm@slu.edu, with copy to editor at ONFEditor@ons.org.

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