INTRODUCTION

In spite of recent advances in molecular biology, breast cancer (BC) remains the most frequently diagnosed cancer in women worldwide. The global incidence of BC rose dramatically to 1.7 million cases between 2008 and 2012 (Kurian, 2010), with 522,000 BC-related deaths recorded. In the United States, close to 231,840 new BC cases were reported in 2015, accounting for almost 29% of the total estimated female cancers recorded that year, with approximately 40,290 deaths from BC that same year, accounting for 14% of the total cancer-related deaths among women (Siegel, Miller, & Jemal, 2015). In Arab countries, the incidences rate has increased dramatically over the past decades with most of the women are diagnosed with BC at advanced stages (Miller, 2010). In Saudi Arabia, BC accounts for around 19.9% of women’s deaths from cancer 27% of all newly diagnosed cancer, and is ranked...
first among cancer-related deaths overall (Hawasaki et al., 2018). The high rate of mortality is due to the development of endocrine resistance and recurrence in BC, with many women relapsing and subsequently dying (Hawasaki et al., 2016). These figures present a major challenge in clinical research and for healthcare systems worldwide. However, mortality could be decreased considerably via prevention strategies aimed at individuals who are identified as being at high risk (Weitzel, Blazer, Macdonald, Culver, & Offit, 2011). Semlali et al in 2018 identified novel single-nucleotide polymorphisms (SNPs) in Toll-like receptor 6 (TLR6) (rs5743810) that are associated with advanced BC risk in the Saudi Arabian population (Semlali et al., 2018).

Mutation in BRCA1/2 is the main cause for 25% of hereditary BC (Easton, 1999), and up to 10% of the total BC cases (Campeau, Foulkes, & Tischkowitz, 2008). Hereditary breast and ovarian cancer (HBOC) syndrome is a major tumor-predisposition syndrome that is mainly caused by pathogenic variants of BRCA1/2 (Petrucelli, Daly, & Pal, 1993). BRCA1/2-driven HBOC is associated with increased risk for several types of cancer, including breast, ovarian, pancreatic, prostate, and melanoma (Ghiorzo, 2014). In a study of 214 families, BRCA1/2 germline pathogenic variants accounted for 80%–90% of familial breast and ovarian cancer (OC) occurrences (Easton, Bishop, Ford, & Crockford, 1993). The relationship between the associated risk of BC, OC, fallopian tube, and primary peritoneal cancers and BRCA1/2 germline pathogenic variants has been verified in several studies, ranging from 16.5% to 87% (Choi et al., 2018).

BRCA have been the subject of extensive research since the mid-1990s. BRCA1/2 are known for their roles as tumor suppressors and are instrumental in regulating double-strand break (DSB) repair, genomic stability, biological pathways that regulate cell-cycle progression, transcriptional regulation, apoptosis, chromatin remodeling, cell growth, and homologous recombination (HR) in response to DNA damage (Narod & Foulkes, 2004; Venkitaraman, 2002).

**THE FUNCTION AND ROLE OF BRCA1/2 IN TUMORIGENESIS**

BRCA1 is located on the long arm of chromosome 17 in the interval 17q12-21 (Hall et al., 1990), while BRCA2 is located on chromosome 13q12-13 (Wooster et al., 1994). BRCA2 is a large encoded protein composed of 3,418 amino acids with 27 exons (Tonin et al., 1996), while BRCA1 is smaller, with 1,863 amino acids and 24 exons (Hall et al., 1990).

**BRCA1** is expressed in most cell types and tissues and is involved in a range of cellular regulatory pathways, including DNA-damage response, cell-cycle progression, regulation of gene transcription processes and ubiquitination. Interactions between BRCA1 and other proteins fulfill key functions in DNA-repair systems: the binding of BRCA1 to CtIP localizes the latter on DNA double-strand breaks, and creates 3’ overhangs of single-stranded DNA (ssDNA). Subsequently, the ssDNA becomes coated with the human replication protein A (RPA), prior to its displacement by the recombinase protein RAD51. At the cell regulation level, the BRCA1 appears as a p21 cyclin-dependent kinase inhibitor, which suppresses the growth of the cell at the G1/S checkpoint.

**BRCA2** is also expressed in most cell types and tissues throughout the body. It maintains its DNA repair mechanisms via multiple interactions: the BRCA2 cyclin-dependent kinase (CDK) phosphorylation site binds to RAD51 to become instrumental in HR and DSB repair. It is essential for BRCA2 to form a complex with a vehicle, partner, and localizer of BRCA2 (PALB2), to penetrate to the center of the nucleus. The N terminus of BRCA2 is considered crucial to the BRCA2–PALB2 complex (Wong et al., 2011).

Several studies have revealed an overlap between BRCA1/2 carriers and cancer outcomes. It has been observed that a higher percentage of triple-negative BC occurred in BRCA1 carriers (Corso et al., 2018). Few studies, however, have observed an association between triple-negative BC and BRCA2 carriers. Reports on the association between pathogenic variants in BRCA1/2 and the poor survival rates associated with BC have been controversial. Women aged 70 years have an 8% chance of developing BC, but susceptibility increases to 65% for BRCA1 carriers and to 45% for BRCA2 carriers (Chen & Parmigiani, 2007). Men who carry BRCA2 are also at increased risk of developing BC (Antoniou et al., 2008; Fentiman, Fourquet, & Hortobagyi, 2006). With regard to OC, 1.4% of females will develop OC, and of the 1.4%, more like 50% prove fatal (Chen & Parmigiani, 2007). However, the percentage of females who will develop OC by the age...
of 70 increases to 39% for those with inherited pathogenic BRCA1 variants and to 11%–17% for women with inherited nontolerated BRCA2 variants (Chen & Parmigiani, 2007).

The risk of developing cancers associated with BRCA1/2 is not limited to BC and/or OC. BRCA1 deficiency increases a woman’s risk of developing peritoneal cancer and fallopian tube cancer (Finch et al., 2006). For men, the risk of developing prostate cancer is heightened by inherited BRCA1/2 pathogenic variants (Levy-Lahad & Friedman, 2007). In both sexes, pathogenic forms of BRCA1/2 were found to increase the risk of developing pancreatic cancer (Ferrone et al., 2009). Additionally, the inheritance of certain BRCA2 biallelic germline alterations has been shown to cause the development of a severe subtype of Fanconi anemia (FA-D1), which is associated with the occurrence of solid tumors and acute myeloid leukemia development in children (Howlett et al., 2002).

3 | LANDSCAPE OF BRCA1/2 VARIANTS IN DRUG RESISTANCE

BRCA1/2-deficient cells and/or cells that exhibit HR have attracted considerable attention with regard to target identification (Bryant et al., 2005). For example, anti-poly ADP-ribose polymerase (PARP) inhibitors (e.g. Olaparib) (Bryant et al., 2005). The efficacy of platinum compounds has also been verified with regard to OC-BRCA1/2 carriers. While these therapeutic agents have been shown to be effective, ultimately, they encounter resistance (Ikeda et al., 2003).

Recently, Venkitaraman (2014) suggested that genome instability caused by DNA repair deficiency following the loss of BRCA1 drives tumor development. This has led to the emergence of a new class of anticancer agents: poly (ADP-ribose) polymerase (PARP) inhibitors. The attachment of PARP-1 to ADP-ribose facilitates the repair of single-strand breaks and results in synthetic lethality. Cells with BRCA1/2 deficiency have high sensitivity to PARP inhibitors (Bryant et al., 2005); however, the majority of patients eventually develops resistance to PARP inhibitors. The mechanisms by which this resistance develops have been investigated: evidence from a murine BRCA1/p53-deficient mammary tumor model has revealed that resistance to PARP inhibitors may be attributable to the up-regulation of P-glycoprotein efflux pumps (Rottemberg et al., 2008). A study conducted by Ikeda and colleagues suggests that secondary somatic BRCA1/2 alteration can reverse cell growth potential, a mechanism by which tumor cells become resistant to cisplatin and PARP inhibitors (Ikeda et al., 2003).

Platinum compounds are very efficient as chemotherapeutic agents for OC. The recurrence-free intervals for OC patients with BRCA1/2 variants, if treated with platinum-based therapy, are much longer than those for patients with sporadic OCs (Boyd et al., 2000). However, the majority of women with OC-BRCA1/2-deficiency experience relapse and eventually develop platinum resistance. Sakai and colleagues verified the in vivo occurrence of secondary variants through the BRCA2-mutated BC cell line HCC1428 (Sakai et al., 2008). Additionally, some clinical data suggest that secondary variants of BRCA1/2 can occur in platinum-resistant OC (Edwards et al., 2008; Swisher et al., 2008).

4 | SYSTEMIC TREATMENT IN BRCA VARIANT CARRIERS

Despite the role played by BRCA in DNA repair, there is currently no in vitro or clinical evidence that individuals with the BRCA variant are more radiosensitive than the individuals without the variant (Lovelock et al., 2007; Nieuwenhuis et al., 2002; Pierce et al., 2000). Gaffney et al. (1998) reported self-limiting moist desquamation in the acute phase after radiotherapy in six of 21 women treated for BRCA-related BC. Likewise, Pierce et al. (2000) compared radiotherapy-related complications in 71 women with BRCA-related BC to those in 213 sporadic controls and observed a similar incidence of acute complications in both groups: 1% of the genetic cohort and 3% of the sporadic cohort exhibited confluent areas of moist desquamation of the skin, indicative of grade 3 reactions. There were no cases of grade 4 skin toxicity. Furthermore, 97% of the genetic cohort and 99% of the sporadic cohort exhibited no change in pulmonary symptoms (Pierce et al., 2000). These observations mirror those of Shanley et al., who found no increase in late toxic effects in 55 BRCA variant carriers, compared with controls who had been treated with radiotherapy. Additionally, a cohort study of 22 patients showed that no BRCA variant carriers had extreme sensitivity to radiotherapy (Leong et al., 2000).

Some side effects of radiotherapy, including fibrosis and vascular damage, may later affect wound healing. These effects should be taken into consideration when young BRCA variant carriers contemplate future therapeutic or cosmetic reconstruction surgery (Trainer et al., 2010). Prophylactic contralateral mastectomy (PCM) considerably reduces the risk of metachronous contralateral BC and may increase the incidence of disease-free survival though this approach has yet to demonstrate a significant increase in overall survival (Lostumbo, Carbine, Wallace, & Ezzo, 2004). However, the tendency toward increased overall survival was noted in a cohort study of familial BC patients who were also BRCA1/2 variant carriers who underwent PCM upon or after their initial cancer diagnoses (McDonnell et al., 2001; van Sprundel et al., 2005).

Despite the efficiency with which MRI surveillance can predict stage-I BC in young women, as well as the increasing uptake of prophylactic bilateral salpingo-oophorectomy (BSO), PCM could potentially increase overall survival of
patients who carry the BRCA variant. However, the decision to undergo PCM is a complex one, particularly with regard to family history, and may reflect a woman’s acceptance of more radical surgery in order to decrease her long-term dependence on breast surveillance methods and the likely eventual need for chemotherapeutic options.

Preliminary studies examining the consequences of genetic testing indicate that if genetic analyses were offered at the time of diagnosis, 52%–100% of patients who tested positive for a variant would choose bilateral mastectomy surgery as their decisive surgical procedure (Schwartz et al., 2004). Furthermore, 24% of patients would select this type of preventive surgery, if they received an “uninformative” BRCA genetic variant result (Schwartz et al., 2004).

Rapid variant testing has a major influence on the locoregional therapeutic options available to patients with no family histories but who display characteristics suggestive of a germ-line BRCA variant (age <40 years and a triple-negative tumor) (Trainer et al., 2010). In individuals with a potential family history of BRCA-related tumors, the value of BRCA variant testing is its ability to identify a family member who does not have cancer but is at high risk of developing the disease in future.

By contrast, and in spite of the crucial information that BRCA variant testing yields, BRCA testing utilization is less immediately used in patients with significant family histories of BRCA-related tumors (Trainer et al., 2010).

BRCA1/2 variants are implicated in the repair of both endogenous and exogenous double-strand breaks throughout HR, and cells with mutant proteins show normal HR repair pathways (Wang, 2007).

It has been recognized that one of the features of BRCA1/2 mutant cells is their hypersensitivity to DNA crosslinking agents, such as cisplatin and carboplatin (Bhattacharyya, Ear, Koller, Weichselbaum, & Bishop, 2000; Evers et al., 2008). Subsequently, it was confirmed that variants within the BRCA2 locus were responsible for Fanconi anemia-D1 (Howlett et al., 2002). Moreover, preliminary data suggest that taxanes, which are used for the adjuvant and advanced treatment of metastatic BC, may not be effective in BRCA carriers (Byrski et al., 2008). Two possible reasons for this are the loss of normal mitotic regulation and taxane-responsive apoptotic pathways that occur as tumors evolve (Lee et al., 1999). It is recommended that a bilateral breast MRI is conducted before surgical or radiotherapy options are decided upon, in the cases of patients who are at increased risk of developing contralateral BC owing to familial disease or BRCA variants (Schwartz et al., 2008).

5 | BRCA VARIANTS PROFILING

The first BRCA1/2 variants were identified in early 1994 (Ford, Easton, Bishop, Narod, & Goldgar, 1994). In recent decades, BRCA1/2 have been extensively screened for more variants, resulting in the identification of several variants associated with different types of cancer susceptibility (Ford, Easton, & Peto, 1995; Wooster et al., 1995). Almost 2,000 distinct variants and sequence variations in BRCA1 and BRCA2 have already been described (Evans, Laloo, Wallace, & Rahman, 2005). The most common variants of BRCA1 and BRCA2 that are found in most populations are 185AGdel and 5382insC, respectively. In BRCA1, large genomic rearrangements (LGRs) account for 27% or less of all gene-associated disorders (Evans et al., 2005). Several BRCA1 pathogenic variants cause a frame-shift variant that leads to complete loss of function, while most reported BRCA2 pathogenic variants are deletions, insertions or nonsense variants that lead to premature (truncated) products (Evans et al., 2005).

The genes in question have heterogeneous variant profiles, as mentioned above. Moreover, different types of variant, with respect to predicted pathogenicity, have been reported. It is not only pathogenic or likely pathogenic changes that harbor BRCA1/2, but also variants of uncertain significance (VUS) (Easton et al., 2015). A study showed that between 10% and 15% of patients who had genetic examination of BRCA1/2 had at least a VUS, representing a major challenge to the provision of proper counseling and cancer risk assessment. Therefore, an advanced reporting and classification system is a key requirement for clinical utility (Plon et al., 2008). In the U.S, VUS frequency differs based on population ethnicity. For instance, African Americans seem to have the highest frequency of VUS (16.5%) (Nanda et al., 2005), while Asian, Middle Eastern and Hispanic populations have less frequency (between 10%–14%) (Nanda et al., 2005).

6 | BRCA1/2 IN PRECISION MEDICINE

Genetic testing in individuals with family histories or who are deemed at risk of developing cancer guides healthcare providers in the development of diagnostics and therapeutic or preventive strategies (Easton et al., 2015). BRCA1/2 are penetrance genes for breast, OC, and tumor-predisposing syndromes. BRCA profiling is associated with clinical utility in the era of precision medicine (Easton et al., 2015). BRCA1/2 profile complexity requires precise and careful interpretation. Some methods have demonstrated their efficiencies in estimating the proportion of risk in an individual with BRCA1/2 pathogenic variants.

BOADICEA uses multiple penetrance BC and OC genes (with its main focus on the BRCA1/2) to predict tumor susceptibility. BRCAPRO and the Manchester scoring system are applied to assess the probability of BRCA variants in families potentially at risk of hereditary BC (Berry et al., 2002). In 2018, the Food & Drug Administration (FDA) approved the first home kit for BRCA1/2 testing (Antoniou et al., 2008).
However, the method only screens three common Eastern European-based variants (Easton et al., 2015).

We believe that all listed approaches have clear limitations, because VUSs, which are common in BRCA1/2, are incompatible with the methods in question. The American Society of Clinical Oncology advocates caution in the interpretation of VUSs in tumor penetrance genes, while recommending the use of effective genetics counseling tools and specialized healthcare practitioners with a view to tailored case management (Easton et al., 2015).

7 | CONCLUSIONS
The relationship between BRCA1/2 and hereditary and familial cancers is indisputable, yet BRCA screening methods are beset with limitations and lack clinical confidence. This review emphasizes the importance of screening BRCA genetics, in addition to their clinical utility. Further, founder variants are anticipated in the Saudi population.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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