Review

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# Genetic testing and counseling challenges in personalized breast cancer care: review article with insights from Türkiye

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According to current evidence, testing for germline *BRCA* pathogenic variants in newly diagnosed breast cancer (BC) patients has the potential to reduce the burden of the disease through targeted therapies and secondary prevention. A personalized approach to testing can lead to improved individual outcomes for patients. Despite the proven clinical utility and therapeutic impact of *BRCA1/2* tests in shaping therapy for metastatic BC, awareness and access to these tests are limited in many developing countries, including Türkiye. This limitation impacts the healthcare economy as delayed or missed interventions can lead to increased long-term costs. The limited access is mainly due to fear of stigmatization among patients, country-specific legislation and costs, a lack of awareness, vagueness surrounding the tests and access restrictions. This review offers a perspective for policymakers and healthcare providers in Türkiye to establish pathways that integrate the patient experience into comprehensive care pathways and national cancer control plans.

**Plain language summary – Importance of gene testing for breast cancer patients:** Recent studies show that testing for a specific gene change in people newly diagnosed with breast cancer can help reduce the impact the disease has on their life as they can be given special treatments. When tests are tailored to each person, they can get better results. However, in many countries, including Türkiye, not many people know about or can get these tests. This is because of concerns about being judged, rules in the country, the cost, confusion about the tests and limited access. Not having these tests can make healthcare more expensive in the long run. This article suggests ways for Türkiye's leaders and health workers to make these tests a regular part of cancer care and planning.

**Tweetable abstract:** Gene testing in new breast cancer patients can reduce disease impact with tailored treatments. Yet, many in countries like Türkiye lack access due to various barriers. Let's integrate these tests into national care plans! #BreastCancer #GeneTesting

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In recent years, the oncological landscape has been transformed by the advent of personalized medicine, emphasizing the identification and targeting of specific genetic markers for cancer prevention, screening and therapeutic interventions. At the forefront of this transformation are the pathogenic variants in the *BRCA1* and *BRCA2* genes, which hold significant implications for hereditary breast cancer (BC). These genetic anomalies are responsible for nearly 30% of inheritable BC cases. For individuals carrying these pathogenic variants, the cumulative risk of developing BC or ovarian cancer (OVC) by age 70 is estimated at 45–66% and 11–41%, respectively [1,2].

The demonstrated effectiveness of screening and preventive measures for *BRCA* mutation carriers has catalyzed a marked increase in *BRCA* testing in recent years. However, in many developing nations, including Türkiye, the routine adoption of these genetic tests for BC patients is not yet widespread, despite the availability of clinical geneticists almost in every city. This shortfall is largely attributed to factors such as limited awareness, insufficient planning of resource utilization, prohibitive costs and insufficient guidance, especially concerning carrier status in healthy individuals. Moreover, the cost-benefit dynamics of these tests can vary significantly based on individual risk profiles, given that the indications and interpretations for non-*BRCA* gene variants aren't as robustly established as those for *BRCA1/2*.

Current literature and guidance on *BRCA* testing emphasize the importance of clinical context and the crucial need to implement it into clinical practice. However, the definitions and recommendations in the related guidelines and consensus papers were developed based on the assumption that all testing standardization and accreditation requirements are met; and all healthcare authorities and related specialists have sufficient knowledge, awareness and referral systems in place. Despite the recommendations from international expert societies provide important guidance to physicians for the diagnosis and treatment of diseases, they may fall short in offering solutions for situations where there is lack of awareness, legislations and systems in place.

This review aims to illuminate the current evidence and guidelines, underscoring the pivotal role of *BRCA1/2* pathogenic variants in determining preventive and therapeutic strategies for patients with metastatic BC. Additionally, it seeks to define the criteria essential for *BRCA* test eligibility. A secondary objective is to delve into and propose potential strategies to address the existing barriers hindering *BRCA* test referrals in Türkiye.

## Cancer preventive & treatment strategies in BC patients with *BRCA1/2* pathogenic variants

Current evidence suggests that testing for germline *BRCA* variants in newly diagnosed patients with BC has the potential to reduce the disease burden through targeted therapies as well as secondary prevention strategies. The latest data and guidelines focus on cancer prevention, screening and follow-up among pathogenic *BRCA1/2* mutation carriers. Pre-testing and follow-up counseling among pathogenic *BRCA1/2* mutation carriers, which outlines screening options for early detection, risk-reducing measures and issues related to fertility in women who have not completed their family, are stated to be essential [3,4].

### Screening

Mammography is the standard screening modality for BC detection, but there is no data indicating that mammography alone reduces mortality in individuals with *BRCA1/2* pathogenic variants [5]. Additionally, false-negative mammography results are common in women with highly densed breast tissue, particularly in younger women. Prospective studies in women at high risk for familial BC have reported higher sensitivity of MRI screening compared mammography, whereas the sensitivity of ultrasound screening appears to be similar to mammography [1]. In a prospective screening trial that evaluated the performance of annual MRI and mammography in 496 *BRCA1/2* mutation carriers between the ages 25–65 years, MRI proved to be more sensitive than mammography (94 vs 77%) [6], especially with regards to detection early-stage tumors. The combined use of digital mammography with digital breast tomosynthesis is currently recommended to improve cancer detection and reduce false-positive call back rates. This is because the appropriate imaging modalities and surveillance intervals are still under investigation, and future prospective trials are needed to evaluate different surveillance strategies for *BRCA1/2* mutation carriers. Since BC is more common at an early age in individuals with *BRCA1/2* pathogenic variants, screening should begin at an early age [4]. Training in breast awareness encompassing regular monthly self-breast examination should begin at the age of 18 for mutation carriers. Additionally, clinical breast examination is recommended every 6–12 months from the age of 25 or 10 years before the youngest BC age diagnosis in the family, whichever is earlier [3,7,8]. Management after 75 years of age should be considered individually, with follow-up continued for people who have had BC without a bilateral mastectomy [4,5]. Recommendations on screening and follow-up for men are different,

Table 1. Screening and follow-up recommendations for individuals with BRCA1/2 mutations.

| Age | Gender | Self-breast examination (monthly) | Clinical breast examination (6–12 months) | MRI (annual) | Mammography. (annual) | USG (±annual) |
|---|---|---|---|---|---|---|
| 18 | Female | | | | | |
| | Male | | | | | |
| 25‡–29 | Female | | | # †† | | |
| | Male | | | | | |
| 30–75 | Female | | | | | † |
| 35–50 | Male | | ‡‡ | | | |
| >75§ | Female | | | §§ | ¶¶ | |
| >50‡,¶ | Male | | | | | |

†Ultrasound may be considered as an adjunct to mammography and as an alternative when MRI is not available at all ages.
‡Or 10 years before the youngest breast cancer diagnosis in the family.
§Treated for breast cancer who have not had bilateral mastectomy.
¶Man with gynecomastia.
#Or individualized based on family history if a breast cancer diagnosis is present before age 30.
††Or starting 10 years earlier than youngest breast cancer diagnosis in the family.
‡‡≥30 years.
§§Individual basis.
¶¶≥70 years, starting 10 years earlier than youngest breast cancer diagnosis in the family annual, others every 3 years.
Data taken from [1,3,4,7,8]
ACR: American College of Radiology; European Society for Medical Oncology; NICE: The National Institute for Health and Care Excellence's; NCCN: National Comprehensive Cancer Network.
NCCN: yellow; ESMO: green; NICE: blue; ACR: red; Not recommended: gray.

as data to support breast screening in *BRCA1/2* mutation carriers is limited. Annual mammogram screening may be considered after 50 years of age or 10 years before the earliest known BC case in the family for men with gynecomastia [3]. Screening and follow-up recommendations for male mutation carriers are summarized in Table 1.

## Risk-reducing surgeries

### *Bilateral mastectomy*

Two meta-analyses showed that prophylactic bilateral mastectomy reduces the risk for BC in individuals with *BRCA1/2* pathogenic variants ([9]: for *BRCA1* and *BRCA2*, RR = 0.134, 95% CI = 0.019–0.937 and RR = 0.183, 95% CI = 0.072–0.468, respectively; [10]: RR = 0.05, 95% CI = 0.02 to 0.1) [9,10]. However, only one of these studies proved significantly reduced mortality (RR = 0.12, 95% CI = 0.04–0.36) [10]. Studies surrounding risk-reducing methods in women with *BRCA1/2* pathogenic variants reported that bilateral risk-reducing mastectomies (RRM) provided a high degree of protection against BC. There is limited data regarding the extend of surgery as a risk-reducing mesure, ranging from total mastectomy, through to skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM), aimed at improving cosmetic results. However, tentative data from Jakub *et al.* [11] showed that NSM was preventive against BC in a *BRCA* population ($p < 0.001$) [11]. Since available data on safety are encouraging and cosmetic outcome is improved, SSM and NSM are accepted alternatives to total mastectomy. Despite there being no clear recommendation on the age of RRM in European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines, as BC risk increases with age, it has been suggested that age and life expectancy should also be considered during RRM decision-making, with the family history of the patients [3,4].

### *Contralateral mastectomy*

Studies on contralateral risk-reducing mastectomy (CRRM) among patients with a previous BC diagnosis showed a significant reduction in contralateral disease, and studies demonstrated a significant reduction in the risk of BC-related death [9,12]. In a meta-analysis, Li *et al.* reported that CRRM significantly decreased the incidence of contralateral BC and overall survival in *BRCA1/2* mutation carriers (RR = 0.072, 95% CI = 0.035–0.148, HR = 0.512, 95% CI = 0.368–0.714, respectively). A retrospective analysis by Metcalfe showed that contralateral mastectomy was also associated with a 48% reduction in death from BC. As the risk for contralateral BC is age dependent the great risk is for those diagnosed at an early age (i.e., <40 years) [12].

### *Salpingo-oophorectomy*

The efficacy of risk-reducing salpingo-oophorectomy (RRSO) for BC in premenopausal *BRCA1/2* mutation carriers has been demonstrated in many studies. Additionally, BC risk reduction was shown to be greater when RRSO was performed at the age of 40 or younger, although the risk reduction was less or no different at the age of 50 and older [4]. In contrast, a recent prospective cohort study suggested that there is no benefit in RRSO with regard to BC risk reduction [4,13]. This issue remains controversial. Therefore, various factors such as the extent of cancer risk reduction/protection, risks associated with surgeries, breast reconstructive options, psychosocial impact and management of menopausal symptoms should be discussed with *BRCA1/2* mutation carriers before deciding on the type of risk-reducing surgery.

## Risk-reducing agents

### *Primer prophylaxis*

There is limited data available for the specific use of selective estrogen receptor modulators and aromatase inhibitors (AI) in individuals with *BRCA1/2* pathogenic variants for primary prophylaxis. An evaluation of the subset of healthy *BRCA1/2* mutation carriers in the Breast Cancer Prevention Trial revealed that BC risk was reduced by 62% in *BRCA2* mutation carriers receiving tamoxifen compared with placebo. However, an analysis of 288 women who developed BC during their participation in this trial showed that tamoxifen use was not associated with BC risk reduction in *BRCA1* mutation carriers [14]. These findings may be related to the greater likelihood of estrogen receptor-negative tumor development in *BRCA1* mutation carriers compared with *BRCA2* mutation carriers. However, the analysis was based on a small number of mutation carriers.

### *Secondary prophylaxis*

There is also limited data on the specific use of these agents for secondary prophylaxis. Most studies have suggested that tamoxifen use reduces the risk of contralateral BC among *BRCA1/2*-associated BC patients. The Hereditary Breast Cancer Clinical Study Group reported that the use of tamoxifen protected *BRCA1/2* mutation carriers affected with BC against contralateral disease by reducing the risk between 45 and 60% [15]. For mutation carriers who also underwent oophorectomy, the data confirming a protective effect was not conclusive [3]. There is little evidence supporting the use of AIs as an effective chemo preventive approach for individuals with *BRCA1/2* pathogenic variants Only a retrospective study published as an abstract reported that AIs may reduce the risk of contralateral BC in women with *BRCA1/2* pathogenic variants [16]. Since there is no evidence that patients with *BRCA1/2*-related BC should be treated differently from patients with non-BRCA-related BC regarding hormone therapy, ESMO and NCCN guidelines recommend adjuvant hormonal therapy to be administered as clinically indicated, regardless of BRCA status [3,4].

## Treatment strategies for metastatic BC

*BRCA1/2* mutant cells experience cell death due to the accumulation of irreparable DNA damage when poly adenosine diphosphate ribose polymerase (PARP) is inhibited. Under normal conditions, DNA is repaired through homologous recombination, a *BRCA* pathway-dependent mechanism [17]. Pre-clinical and clinical trials have demonstrated that inhibiting PARP renders tumors devoid of *BRCA* function extremely sensitive [18–20].

Two PARP inhibitor monotherapies, olaparib and talazoparib, have been approved by the US FDA and European Medicines Agency (EMA) for use in deleterious or suspected deleterious g*BRCA*-mutated, human epidermal growth factor receptor 2 (HER2)-negative metastatic BC, based on positive outcomes in phase III trials (OlympiAD and EMBRACA) [21–24]. In the OlympiAD study, olaparib showed a 3-year disease-free survival advantage (85.9 vs 77.1%; $p < 0.001$) and improved progression-free survival compared with chemotherapy (7.0 months

vs 4.2 months; hazard ratio for disease progression or death, 0.58; 95% CI: 0.43 to 0.80; $p < 0.001$). The response rate was 59.9% in the olaparib group and 28.8% in the chemotherapy group in patients with a germline *BRCA1/2* pathogenic variants and *HER2*-negative metastatic BC [25]. In the EMBRACA study, chemotherapy was compared with a different oral PARP inhibitor, talazoparib. Talazoparib prolonged progression-free survival (hazard ratio [HR] 0.542, 95% CI: 0.413–0.711; $p < 0.0001$) and improved patient-reported outcomes in germline *BRCA1/2* mutated advanced BC patients. The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6 vs 27.2%; odds ratio, 5.0; 95% Cl: 2.9 to 8.8; $p < 0.001$) [26]. However, the final analysis of these studies reported that none of these agents prolonged overall survival which was secondary end point, compared with chemotherapy [27,28]. Therefore, guidelines recommend assessing germline *BRCA1/2* pathogenic variants in all patients with recurrent or metastatic BC to identify candidates for PARP inhibitor therapy [29,30].

Although PARP inhibitors are typically recommended as a first-line treatment for metastatic disease in individuals with germline *BRCA* pathogenic variants who have received chemotherapy in the (neo)adjuvant period, chemotherapy is still the preferred option for those who have never been exposed to either treatment in the early or metastatic period and have progressed while using a PARP inhibitor [29]. Of course, those with visceral crisis should be added to this group. For patients with *BRCA*-associated BC that also expresses PD-L1, immunotherapy plus chemotherapy is recommended as the initial chemotherapy regimen compared with other chemotherapy options [29]. However, for those with *BRCA*-associated, PD-L1-negative tumors, both platinum-based drugs and taxanes are considered viable options for chemotherapy [29]. Platinums are preferred in this scenario, as they cause DNA chain breaks, similar to other solid tumors with *BRCA* pathogenic variants.

Based on the results, guidelines have updated their recommendations regarding PARP inhibitors in adjuvant therapy for BC patients with *BRCA* pathogenic variants. Adjuvant olaparib is recommended for *BRCA* carriers with residual disease and CPS + EG $\geq$3, in triple-negative BC patients with residual disease after neoadjuvant therapy, and also for patients with N2 disease and hormone receptor-positive disease treated with adjuvant chemotherapy. In addition, talazoparib showed a 53% RCB-0 (residual cancer burden) rate without chemotherapy in the neoadjuvant setting. Clinical studies are still ongoing [31].

Although olaparib and talazoparib are FDA-approved for use in HER2-negative disease, the NCCN panel supports their use in any BC subtype associated with a germline *BRCA1* or *BRCA2* pathogenic variants [29].

## Assessment of risky populations by BRCA1/2 testing

With the increasing use of multigene panels, detection of *BRCA1/2* and other important familial pathogenic variants has become more common among individuals with risk factors and cancer patients. The available literature and expert consensus suggest evaluating patients based on their personal and familial factors before initiating *BRCA1/2* screening in the population.

### Personal factors

#### *Early age*

Studies have shown that the history of BC is more prevalent at earlier ages in *BRCA1/2* mutation carriers compared with the normal population. The prevalence of *BRCA1/2* pathogenic variants in women with BC is higher in patients aged 30–45 years. For this reason, *BRCA1/2* mutation testing is recommended in women with BC under 45 years of age by oncology guidelines [1,3,4]. In Türkiye, the mean age was reported as 41–43.7 in *BRCA1/2* mutation carriers, and it was previously shown that 76.6% of BC patients with *BRCA1/2* pathogenic variants were diagnosed before the age of 45 [32,33].

#### *Ethnicity*

Certain populations exhibit a higher likelihood of harboring genetic pathogenic variants than the general population. In an Ashkenazi Jewish population in Israel, the prevalence of *BRCA* pathogenic variants was 34%, and in those with family increased to 55% [34,35]. Due to the high prevalence, *BRCA1/2* mutation testing is recommended for all women of Ashkenazi Jewish heritage affected with the disease regardless of age [3,4]. Data regarding *BRCA* mutation prevalence for Türkiye is highly variable. According to a recent study, the prevalence of these pathogenic variants was 20.66% in BC patients compared with 22.61% in clinically unaffected individuals [36]. Older studies have reported a mutation frequency ranging between 9.4–19.0% in different high-risk populations of Türkiye involving individuals with either a personal or family history of the disease [32,33,37]. These variations are thought to be influenced by the different ethnic groups in specific regions in Türkiye.

### *Bilaterality*

Multiple or bilateral primary tumors are more common in hereditary BC compared with sporadic tumors. These patients with *BRCA1/2* pathogenic variants are reported to be at an increased risk of contralateral disease (38.5%) [38]. Currently, the estimate of cumulative risk for contralateral BC 20 years after initial BC diagnosis for *BRCA1* mutation carriers is 40% whereas for *BRCA2* it is 26% [38]. Bilateral BC incidence was previously reported as 27% in BC patients with *BRCA1/2* pathogenic variants (16.2 vs 10.8% in *BRCA1* vs *BRCA2*, respectively) in Türkiye [32].

### *Gender*

Male breast carcinoma accounts for less than 1% of all BC cases [39]. Hereditary BC is more common in men and women with a family member with male BC [40]. A retrospective study has demonstrated that the cumulative risks of male BC were higher in both *BRCA1* and *BRCA2* mutation carriers than in non-carriers at all ages. Also, *BRCA2* germline variants are more common than those in *BRCA1* in male BC patients [39]. Consequently, *BRCA1/2* mutation testing is recommended for all male BC patients as stipulated by the guidelines. In Türkiye, the male BC incidence was reported as 1.9%, where the *BRCA1/2* mutation rate was 18.2% in the male BC population, with a higher prevalence of *BRCA2* variant than *BRCA1* variant, which was consistent with the literature (4.6 vs 13.6%) [32].

### *Histology*

*BRCA1*-positive tumors often exhibit triple-negative features with a basal-like gene expression profile and express cytokeratin 5/6, cyclin E, and p5341. However, *BRCA2*-mutant BC tumors have shown to be equally common in all subtypes but are usually high-grade, estrogen-receptor positive, and HER2-negative [41]. The prognosis of BC patients with *BRCA1/2* pathogenic variants is controversial in the literature. The POSH prospective study showed no significant difference in overall survival or distant disease-free survival between patients carrying *BRCA1/2* pathogenic variants and patients without these variants after a diagnosis of BC [42]. Among triple-negative breast carcinoma patients in Türkiye, *BRCA1/2* mutation prevalence was 24.2% in patients younger than 60 years old and 37.5% in those younger than 40 years old [33].

Based on the available evidence, guidelines strongly recommend germline *BRCA* testing in all BC patients with triple-negative features, regardless of family history, and hormone-positive patients with risk factors [1,2].

## Familial factors

Advances in molecular genetics have identified a number of genes associated with inherited susceptibility to breast, ovarian and pancreatic cancers (e.g., *BRCA1/2*, *PALB2, TP53, CDH1*) [3]. Genetic tests that characterize the specific pathogenic or likely pathogenic variant present in these genes in certain individuals and families implies an increased risk for these cancer types. Among these, the presence of *BRCA1* and *BRCA2* variants confer the highest risk [43]. Although pathogenic *BRCA* variants are rare in sporadic BC, they are responsible for 90% of hereditary breast and ovarian cancer syndromes inherited by an autosomal-dominant transition [43]. Germline mutations in these genes confer an increased lifetime risk for a number of malignant tumors, especially breast and ovarian cancer, but also pancreatic, prostate cancer, stomach, laryngeal and cancer of the fallopian tube [43]. According to population studies, individuals with hereditary breast and ovarian cancer syndrome have a lifetime risk of developing BC of 50–80% and of 30–50% for ovarian cancer, respectively [44]. Guidelines have defined risky situations as defined in Table 2, according to the results of studies to identify individuals who may be the *BRCA1/2* mutation carriers due to a family history of cancer [1,3].

On the other hand, multigene testing for cases with hereditary predisposition can alter the clinical approach for the patients and their families. Although 'intermediate' penetrant (moderate-risk) BC-associated genes have limited data with no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants, the risks may not be entirely due to that gene alone. Moderate-risk genes may be influenced by gene-gene interactions, or certain genetic alterations on these genes may have a higher or lower risk for pathogenicity [45]. Among these moderate-risk genes; *ATM, BARD1, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11* and *TP53* were related to an increased risk of BC, while *BRIP1, MSH2, MLH2, MSH6, PMS2, EPCAM, RAD51C* and *RAD51D* genes' BC risk is not completely known yet due to insufficient evidence. Nevertheless, these potential BC risk genes should not be overlooked in *BRCA1/2* negative familial cases [45].

**Table 2. Characteristics of individuals with BRCA1/2 mutation risk.**

| | | |
|---|---|---|
| Age at diagnosis/family history | <45y | ≥1 close blood relative with breast cancer |
| | 46–50y | Unknown or limited family history<br>Multiple primer breast cancers<br>≥1 close blood relative with breast, ovarian, pancreatic or prostate cancer at any age |
| | >51y | ≥1 close blood relative with any<br>• breast cancer at age ≤50 y or male breast cancer at any age<br>• ovarian cancer any age<br>• pancreatic cancer any age<br>• metastatic, intraductal/cribriform histology, or high- or very-high risk group prostate cancer any age<br>• ≥3 total diagnoses of breast cancer in patient and/ or close blood relatives<br>• ≥2 close blood relatives with either breast or prostate cancer (any grade) at any age |
| | Any age | Triple negative breast cancer<br>Lobular breast cancer with personal or family history of diffuse gastric cancer<br>Male breast cancer<br>≥1 close blood relative with male breast cancer |
| By Ancestry | | Ashkenazi Jewish ancestry |

Data taken from [1,2].

## Principles of genetic counselling, current barriers & unmet needs in *BRCA1/2* testing

Cancer genetics plays a crucial role in managing individuals with inherited or family-related cancers, encompassing prevention, detection and therapy. Determining someone's risk for these types of cancers involves a detailed review of their personal and family medical histories. Primary care professionals can utilize recognized familial risk assessment tools, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer Cuzick) and brief versions of BRCAPRO, to determine the need for in-depth genetic counseling. These tools are proven to effectively gauge the probability of an individual having a *BRCA*1/2 gene variant. If these tools indicate a risk, a deeper genetic counseling session is recommended [46].

The process of genetic counseling includes detailed kindred analysis and risk assessment for potential germline *BRCA1/2* variants. It also involves identifying candidates for testing, patient education, discussing the benefits and harms of genetic testing, interpreting results after testing and discussing management options. Although the predisposition assessment enlightens the path for genetic testing and patient management, it should not be forgotten that genetic counseling can also help women who have an indeterminate family history of BC develop a more accurate view of their risks [47]. Pre- and post-test recommendations for a person referred for *BRCA1/2* mutation testing are summarized in Figure 1.

Despite the substantial need to identify patients at risk for genetic variants to implement risk-reducing screening and interventions, available literature indicates that an alarming number of patients with genetic variants do not receive recommended genetic counseling, testing, or interventions [1,3,4]. The barriers and unmet needs in *BRCA1/2* testing from a global and Turkish clinical perspective are summarized below and in Figure 2.

### Lack of awareness

The benefits of genetic counseling, early diagnosis, prevention and treatment strategies in *BRCA1/2* mutant individuals are not sufficiently known by societies or healthcare professionals worldwide [48–50]. Similarly, in Türkiye, there is limited genetic knowledge, a lack of attention to family history and a lack of awareness of the importance of *BRCA* variants in follow-up and treatment in primary and secondary care, except for geneticists [51]. Genetic counseling with geneticists is, therefore, very important. These barriers lead to low referral rates in pre-/post-test genetic counseling and result in unequal testing access. The inadequacy of current international and local *BRCA* genetic testing guidelines to identify eligible patients is also a major barrier for healthcare professionals.

### Fear of being stigmatized

The perception of this subject varies among societies with different socio-cultural structures [46,48,52]. In Türkiye, patients may experience constant anxiety about cancer, marriage, having children regarding the possibility of genetic transmission, difficulty in adopting and fear of being abandoned by their partner. Being a mutation carrier can also be perceived as being a contagious disease carrier in Türkiye, and individuals may be exposed to genetic discrimination at work or in their social environment. Therefore, high-risk individuals may refuse to be tested due

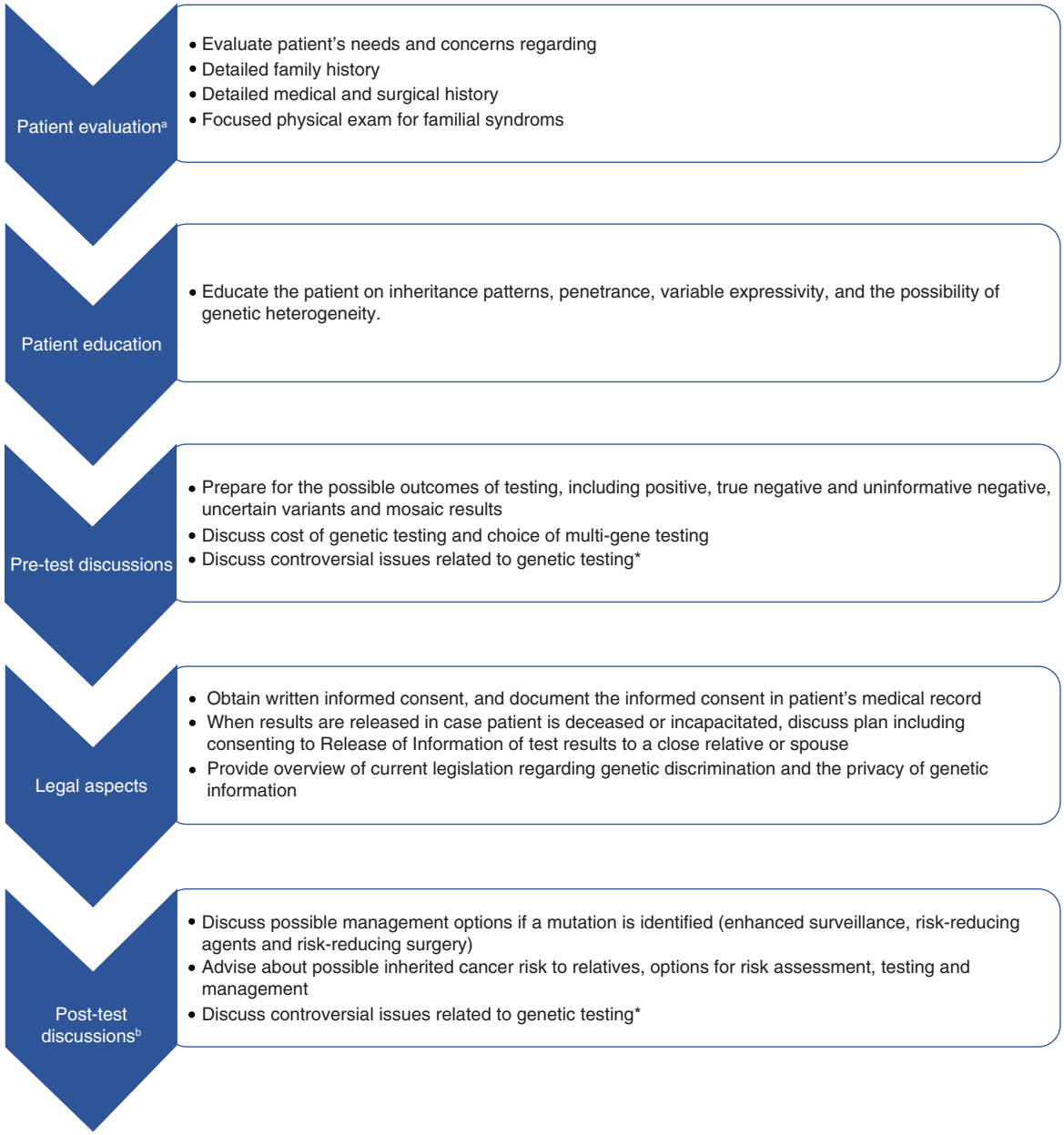


**Figure 1. Principals of pre and post-test genetic counselling.**
[a]Refers to Table 2 within the text.
[b]Refers to Table 1 within the text.
*In children younger than 18-year-old genetic testing is generally not recommended when results would not impact medical management. Patients who have received an allogeneic marrow transplant or with active or recent hematologic malignancies should not have molecular genetic testing via blood or buccal samples. Significant limitations of interpreting test results should be discussed.
Data taken from [3].

to the fear of being stigmatized by relatives, friends, partners and employers after being reported as a mutation carrier.

This topic may also trigger ethical discussions in different settings. Do physicians have the responsibility to warn 'at-risk' relatives [48,53,54]? Will this be ethical or not? How will the confidentiality of the doctor-patient relationship be protected? How should a counselor guide a mutation carrier who chooses not to share genetic information? Providing appropriate counseling to such people is one of the toughest challenges experienced by physicians in

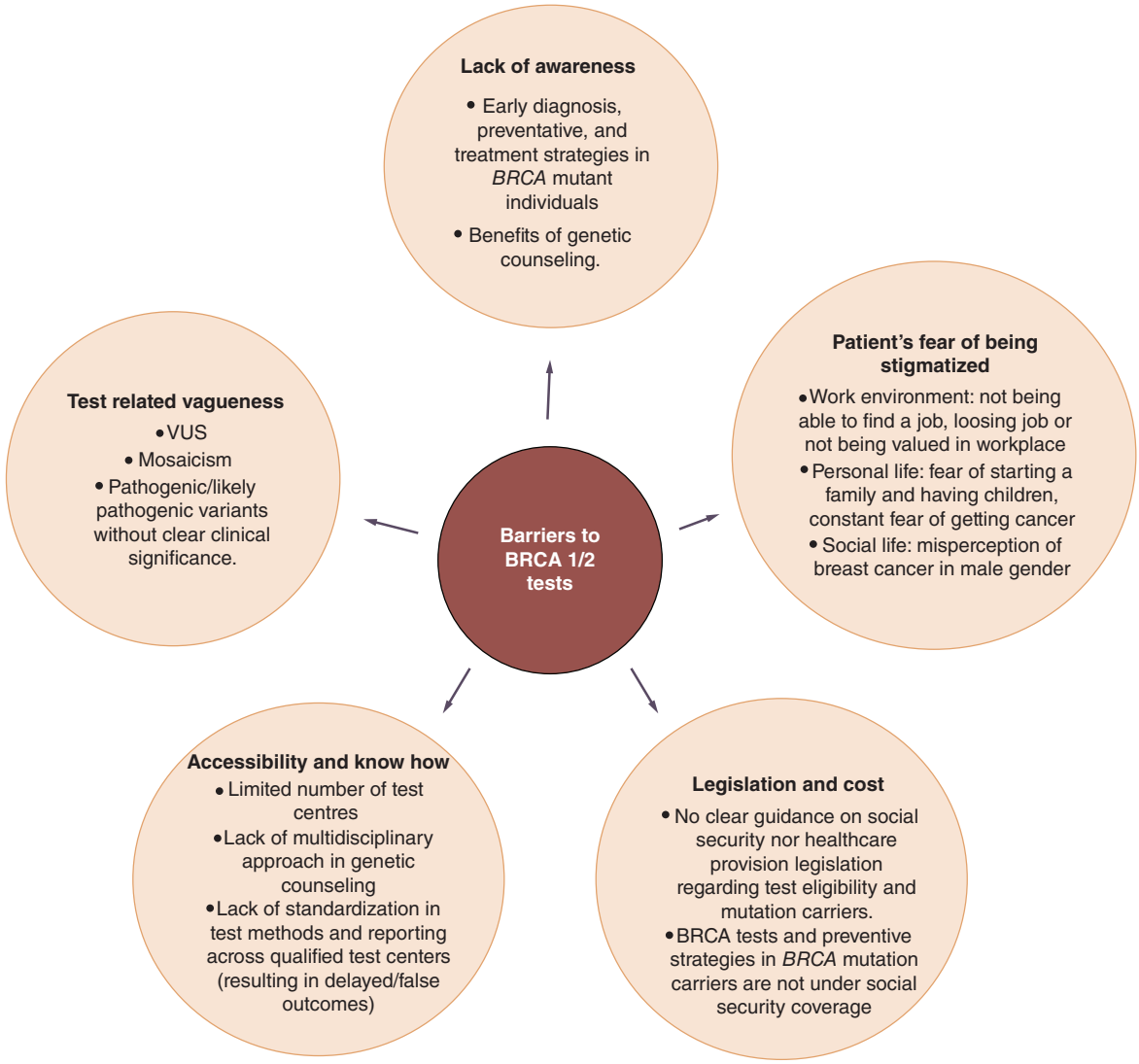


**Figure 2. Barriers and unmet needs in BRCA1/2 testing.**
VUS: Variants of uncertain significance.

terms of ethics for public health. Also, the question of "which physician group should provide the follow-up and manage *BRCA* mutation carriers?" is important. It is still controversial whether the specialist group that should follow-up non-patient carriers should be oncologists, family physicians, medical geneticists, or whether a brand-new concept/group of experts should be involved in this process. The fact that individuals in this group cannot be referred to a specific and well-defined group of experts seems to be a significant barrier.

## Legislation & cost

Various countries have legislation and regulations to protect against discrimination, but there is no clear guidance within social security legislation and healthcare provision legislation in Türkiye regarding the genetic test eligibility or mutation carriers [55–57]. In addition, *BRCA* tests and preventive strategies in *BRCA* mutation carriers are not fully under social security coverage. On the other hand, being a mutation carrier is not taken into account while calculating the insurance premiums for social security and private health insurance.

## Test-related vagueness & access restrictions

Genetic tests have inherent challenges; results can be delayed, there may be false outcomes, variants of uncertain significance (VUS), mosaicism and pathogenic/likely pathogenic variants without clear clinical significance, which

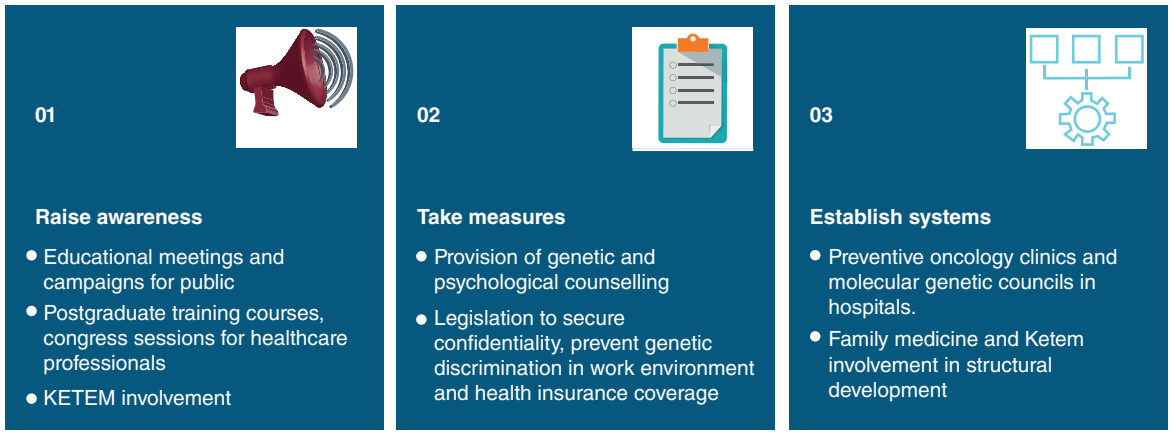


**Figure 3. Recommendations to overcome barriers in genetic testing.**
KETEM: Early Diagnosis, Screening and Education Center for Cancer.

can be frustrating [48]. In addition to access restrictions, there is also a lack of standardization in test methods and reporting across qualified test centers in Türkiye. Moreover, there is no clear local guidance on risk management for carriers of pathogenic/probably pathogenic variants. Therefore, genetic counseling for *BRCA1/2* mutation testing should be performed by multidisciplinary teams, including a genetic counselor, clinical geneticist, oncologist, surgeon, oncology nurse, or other healthcare professionals suitably trained by primary care clinicians. This multidisciplinary approach needs to be established and continuously evolve in Türkiye, as in any part of the world.

## Discussion

Despite the proven clinical utility and therapeutic impact of *BRCA1/2* tests in shaping therapy for metastatic BC, awareness and access to these tests are still limited. Based on the reviewed literature and discussed barriers in previous sections, several strategies to improve access in Türkiye are interpreted and formulated as follows (Figure 3).

Educational meetings and awareness day campaigns on genetics and *BRCA* variants can be organized with the support of the Ministry of Health and non-governmental organizations through social media and public broadcasting by means of radio or television or the internet programs to raise awareness within society. Postgraduate training courses and congress sessions emphasizing post-test genetic evaluation, explaining the follow-up pathway, and the family genetic tree, etc. in *BRCA1/2* positive individuals would be beneficial for family medicine, general surgery, general internal medicine and oncology branches. The Early Diagnosis, Screening and Education Center for Cancer (KETEM) is a new initiative introduced by the Turkish Ministry of Health (MoH) [58]. KETEM's most important goals are stated as follows: to raise awareness about cancer in society, to prevent cancer and to carry out screenings by informing people about prevention methods and screening programs through face-to-face trainings. Despite the KETEM concept still being under development, it has the unlocked potential to be an important platform for multidisciplinary collaborations.

When considering issues related to genetic discrimination and social stigmatization, it is important to provide genetic counseling and psychological support to individuals with *BRCA* pathogenic variants and their partners by explaining the characteristics of the *BRCA* variant, the fact that not all mutation carriers develop cancer, and the importance of early diagnosis and preventive strategies. *BRCA* mutation testing could be offered to couples before marriage to prevent post-marital problems, similar to premarital thalassemia testing. High-risk individuals or those with *BRCA1/2* pathogenic variants who consult with gynecologists about family planning should be referred to genetic counseling to gain a better understanding of prenatal genetic testing. To prevent genetic discrimination in social and business contexts, it is important to explain that having a *BRCA*1/2 pathogenic variant is not a disease or contagious, and only increases the risk of BC compared with the general population.

The confidentiality of the doctor-patient relationship is mandatory, both legally and ethically [59]. Genetic information cannot be shared with anyone without the consent of the individual [59]. However, as knowledge and demand for genetic testing grow around the world, physicians are sometimes forced to make difficult decisions and breach confidentiality to provide required information regarding risks and risk-reduction measures. In the USA, the Health Insurance Portability and Accountability Act (HIPAA) and most medical societies agree that

although physicians have a duty to advise patients and their relatives on the relevance of genetic information, it is not their duty to violate patient confidentiality and directly warn patients' relatives [48,59]. Therefore, health professionals require training and support to discuss genetic risks with individuals and all family members. The Genetic Information Nondiscrimination Act (GINA) was passed in the USA in 2008 to protect individuals from discrimination by health insurers and employers on the basis of genetic information. GINA prohibits insurance companies from taking into account genetic conditions or family history when determining risk assessment, thus protecting mutation carriers from paying higher insurance premiums or being denied health coverage. GINA also prohibits employers from making employment and promotional decisions based on genetic information, imposing fines of up to US$300,000 per violation [55,57]. Such legal arrangements can also be made in Türkiye.

It can be challenging to provide a specific recommendation for delayed results. As awareness of *BRCA* pathogenic variants increases among physicians and patients, the required number of patients per test cycle will be achieved in a shorter period of time. There are numerous genetic testing companies in the market, so genetic tests must be reliable and standardized as any other laboratory tests. Expert supervisory boards should be established, and only internationally verified tests should be used to standardize the process and reporting. Fear and anxiety may develop in individuals with VUS and mosaicism, as these may become pathogenic later on. For post-test genetic evaluation, patients can be referred to medical geneticists, and psychological support should also be provided to these individuals.

After the test results are out, most centers share them with individuals and doctors via text messages and/or emails. This can be disseminated, and information can be sent to the clinical geneticist at hospitals where the individuals are affiliated. The issue of which physician group should adopt the follow-up and management of *BRCA* mutation carriers has not yet been clarified. Establishing preventive oncology clinics and expanding molecular genetic councils in hospitals may increase the interaction between disciplines. In addition, the Turkish Ministry of Health can expand the preventive medicine duties of family physicians by including *BRCA* mutation carrier follow-up programs within key performance indicators (such as pregnancy follow-up and vaccination). The KETEM platform can also be positioned in this structural development. Thus, referral of carrier individuals to their regular clinical geneticist can be encouraged. One of the most significant advantages in Türkiye compared with many countries worldwide is that there is a clinical geneticist in almost every city. When patients are referred by KETEM, family physicians, or other specialists, they can easily apply to Genetic Diseases Evaluation Centers for the interpretation of genetic tests performed in external centers and for further assessments if necessary.

## Conclusion

The broader implications of enhancing *BRCA* testing in Türkiye cannot be understated. From a theoretical perspective, increased access and awareness of *BRCA* testing would lead to a more informed populace, better equipped to make decisions about their health. Adopting a personalized approach to testing and treatment can significantly lead to improved individual outcomes. This would not only potentially reduce the incidence of late-stage BC diagnoses but also empower individuals to proactively address concerns related to cancer prevention, early detection, lifestyle modifications and potential genetic implications for their offspring.

Such empowerment can lead to proactive health behaviors, early interventions and tailored treatment plans, ultimately improving patient outcomes and reducing the burden on the healthcare economy. Furthermore, a society more attuned to the importance of genetic testing would likely experience a cultural shift, where genetic health becomes a shared responsibility, fostering community support and reducing stigmatization.

Low referral rates and unequal *BRCA* testing is a significant issue in Türkiye from our expert perspective, however, there is no data on referral rates nor on testing. Therefore, there is a need for further studies to understand the exact burden on this issue.

In conclusion, this review provides a foundation for discussions with policymakers and healthcare providers in Türkiye to establish pathways and policies that integrate the patient experience into comprehensive care pathways and national cancer control plans.

## Future perspective

As of the writing of the above article, the access and awareness of *BRCA* testing for newly diagnosed patients with BC in many developing countries, including Turkiye, will probably be still limited due to various factors. However, it is likely that in the next 5–10 years, we will see significant improvements in the availability and accessibility of *BRCA* testing globally.

Advancements in technology and research will likely lead to more affordable and efficient testing methods, making it easier for patients to access and obtain necessary testing. Additionally, increased public education and awareness campaigns, as well as changes to legislation and healthcare policies, may help reduce the stigma and barriers associated with genetic testing, thereby increasing the number of individuals who undergo testing.

Moreover, as more data is collected on the efficacy of targeted therapies and secondary prevention for individuals with *BRCA* pathogenic variants, it is likely that these treatments will become more widely available and incorporated into standard cancer care pathways. This could potentially lead to better outcomes for patients with BC and other *BRCA*-related cancers.

Overall, it is expected that in the next 5–10 years, there will be significant progress in the *BRCA* testing field, with increased access, awareness and integration of genetic testing into cancer care pathways, leading to improved outcomes for patients.

## Executive summary

**Cancer preventive & treatment strategies in breast cancer patients with *BRCA1/2* pathogenic variants**

**Screening**

- MRI screening detects breast cancers better in high-risk women than mammography.
- Digital mammography with tomosynthesis improves cancer detection.
- Surveillance strategies for *BRCA1/2* carriers need future evaluation.
- Early screening is crucial due to higher early-onset breast cancer risk in *BRCA1/2* carriers.
- Monthly self-breast examination is recommended.

**Risk-reducing surgeries**

- Bilateral mastectomy offers significant protection against breast cancer.
- Age and family history are vital when considering mastectomy.
- Risk-reducing salpingo-oophorectomy reduces risk in premenopausal breast cancer patients with *BRCA1/2* pathogenic variants.

**Risk-reducing agents**

- Tamoxifen reduces contralateral breast cancer risk in *BRCA1/2* patients.
- Aromatase inhibitors may reduce contralateral breast cancer risk.

**Treatment strategies**

- PARP inhibitors, like olaparib, are approved for certain *BRCA*-mutated breast cancers.
- Platinum-based drugs are options for chemotherapy in *BRCA*-associated tumors.

**Assessment of risky populations by *BRCA1/2* testing**

- Early age and certain ethnicities have higher *BRCA1/2* mutation likelihood.
- Male breast cancer patients should undergo *BRCA1/2* testing.
- Familial factors play a role in *BRCA*1/2 mutation risk.

**Principles of genetic counseling, current barriers & unmet needs in *BRCA1/2* testing**

- Primary care clinicians should use familial risk assessment tools.
- Barriers include lack of awareness, fear of stigmatization and legislative restrictions.
- Multidisciplinary teams are essential for effective genetic counseling.

**Discussion**

**Strategies to improve access to *BRCA1/2* tests**

- Raise societal awareness through campaigns and training.
- Genetic counseling and psychological support are crucial.
- Legal measures can protect against genetic discrimination.
- Family physicians should include *BRCA* follow-up in performance indicators.

**Challenges in genetic testing**

- Tests should be standardized.
- Support is needed for individuals with uncertain results.

**Follow-up & management of *BRCA* mutation carriers**

- Preventive oncology clinics can foster interdisciplinary interaction.
- Referral to genetic physicians is encouraged for carrier individuals.

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I Cicin made contributions to the design of the work, all authors provided input and revised and approved the final manuscript.

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