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Genetic Considerations in the Locoregional Management of Breast Cancer: a Review of Current Evidence

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Abstract

Purpose of Review Breast cancer is the most commonly diagnosed cancer and is the second leading cause of cancer death in women. Breast cancer screening has significantly improved detection of cancer and reduced mortality however, mortality has plateaued in recent years. As such, identifying ways to improve management decisions to further reduce mortality remains a high priority. Herein, we review the current evidence for locoregional management recommendations in patients with hereditary breast cancer mutations. Additionally, we discuss the potential utility of gene assays in locoregional management decision-making.

Recent Findings Gene assays are currently used to identify patients who would benefit from systemic adjuvant therapy, and their uptake has improved clinical outcomes. There is growing evidence supporting their utility in determining patients at a higher risk for locoregional recurrence. As such, gene assays may have a role in decision-making regarding the locoregional management of breast cancer, and specifically the use of adjuvant RT.

Summary Risk reduction is central to the management of patients with hereditary breast cancer mutations. In patients with BRCA1/2 mutations, risk-reducing mastectomy (RRM) ± adjuvant radiotherapy (RT) or breast conserving therapy (BCS) with adjuvant RT is often an appropriate treatment regimen. A similar treatment approach is likely appropriate in other high-penetrance mutations, although RT should be used cautiously in patients with TP53 mutations. In patients with low-moderate penetrance mutations, BCS with adjuvant RT or RRM in conjunction with patient preference is likely appropriate, although RT should be avoided in patients with ATM mutations.

Keywords Breast cancer · Hereditary · BRCA · Gene assay · Locoregional management

Introduction

Breast cancer remains the most commonly diagnosed cancer, with over 1 in 8 women expected to develop breast cancer over the course of their lifetime [1]. In 2021 alone, it was estimated that over 280,000 cases of breast cancer would be diagnosed [1]. Additionally, breast cancer remains the second leading cause of cancer death in women [1]. Although screening paradigms have greatly increased breast cancer detection and thus reduced mortality, progress has plateaued — mortality reductions in breast cancer have slowed in recent years [1, 2•]. Further, recurrence remains a significant issue in women diagnosed with breast cancer, with up to 10% of patients having locoregional recurrence following treatment [3–7]. As such, identifying areas of potential improvement in management decisions to reduce the burden of recurrence and subsequent mortality is of high priority. A potential area of continued investigation is the use of genetic testing to guide management decisions in an expanded number of women diagnosed with breast cancer.

Currently, genetic testing is routinely done with the goal of identifying hereditary mutations associated with breast cancer, such as the *BRCA1/2* genes, in individuals with a family history of breast cancer, family history of related cancers, early onset breast cancer, and triple negative breast cancer, among other criteria [8••, 9]. Hereditary breast cancers represent about 10% of all diagnosed breast cancer, although women with these mutations often have a higher burden of disease and may be more likely to have triple negative cancer which carries a poorer. prognosis [10–13]. The goal of this review is to discuss

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the current management of hereditary breast cancers and the expanding role of genetic factors as a potential additional datapoint on which to base locoregional management decisions in women without hereditary cancer syndromes.

Hereditary Breast Cancer

Current Genetic Testing Recommendations

As mentioned above, the current goal of genetic testing is to identify women with hereditary mutations that increase their risk for breast cancer. The National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing in individuals as shown in Table 1 [8••]. US Preventive Services Task Force (USPSTF) recommendations are similarly indicated in individuals with breast cancer and a concerning family history of cancer [14]. Based on these recommendations, a minority of individuals with breast cancer are screened, and an estimated 50–80% of individuals with breast cancer do not undergo screening [15, 16]. It is also estimated that the majority of *BRCA1/2* carriers have not been identified [17•, 18]. Within individuals who do not undergo screening, one study estimates up to 8% are carrying a known pathogenic mutation, comparable to the 9% of individuals found to have a pathogenic variant who meet the criteria for genetic testing [19••]. As such, expanding testing criteria may lead to increased rates of identifying pathogenic mutations in individuals diagnosed with breast cancer, although future studies are required to fully elucidate the impact of additional genetic testing on clinical outcomes [19••, 20].

To that end, some have argued in favor of universal testing for all women who have been diagnosed with breast cancer [21]. Universal testing would significantly increase the rate of identifying pathogenic mutations and thus may change management for a proportion of women diagnosed with breast cancer, which is discussed below [22–25]. Further, the cost and accuracy of genetic testing for hereditary mutations associated with breast cancer have improved in recent years [26]. Additionally, in conjunction with genetic counseling, the knowledge of a hereditary mutation associated with breast cancer has been shown to have a significant impact on patient decision-making regarding surgical treatment [27–29]. Finally, pre-operative genetic testing has not been found to delay appropriate surgical treatment [30]. However, universal testing does still present challenges, namely, variability between clinically available tests, the potential subsequent need for an increased number of genetic counselors, and the high rate of detection mutations of unknown clinical significance that do not currently have associated treatment recommendations [31].

Management Considerations for Hereditary Breast Cancer

The importance of the current paradigm for genetic testing is to change management in women with hereditary mutations associated with breast cancer. Mutations such as *BRCA1/2* have a large body of evidence for appropriate recommendations for management, yet there is less evidence in the current literature regarding the management of other genes known to be associated with the development of breast cancer. However, regardless of the mutation present, women with hereditary cancers are often managed in ways that are not fully concordant with existing guidelines compared to individuals without mutations present [32•]. As such, it is important to identify and raise awareness of appropriate and effective treatment regimens in individuals with these hereditary mutations. Although the management of breast cancer involves shared decision-making between patient and provider, providing evidence-based recommendations for effective treatments is still crucial [33, 34]. We summarize treatment recommendations in patients with hereditary cancer mutations in Table 2.

BRCA1/2

Breast cancer susceptibility genes 1 and 2 (*BRCA1/2*) are crucial for tumor suppression, specifically promoting

Table 1 National Comprehensive Cancer Network (NCCN) guidelines for genetic testing

Patients who should undergo genetic testing
• Individuals with a blood relative with a known breast cancer-associated mutation
• Individuals with cancers diagnosed younger than age 45
• Individuals diagnosed below age 50 but with another previously diagnosed breast cancer, unknown or limited family history, or a relative with breast, ovarian, pancreatic, or prostate cancer
• Those diagnosed below age 60 but with triple negative breast cancer
• Male individuals diagnosed with breast cancer
• Individuals of any age with Ashkenazi Jewish ancestry or a close relative diagnosed under age 50
• Individuals with a personal history of pancreatic, ovarian, or prostate cancer
• Individuals with a family history of cancer and who meet the above criteria, or individuals with a high likelihood of having a BRCA1/2 mutation using available probability modeling
• Individuals meeting the criteria in 1–3 but who were previously only tested using single-gene testing and were negative

Table 2 Cancer risk and locoregional management recommendations in hereditary breast cancer mutations

Mutation	Lifetime breast cancer risk	Recommended treatments
BRCA 1/2	> 60%	• Mastectomy and SLNB in breast with malignancy plus CRRM without SLNB is effective in reducing recurrence risk • BCS with adjuvant RT is effective in reducing recurrence, but still carries a higher recurrence risk than the above treatment
High penetrance genes		
TP53	> 60%	• Mastectomy with CRRM effective for reducing recurrence risk • Elevated risk of RT associated cancers • RT may be considered in those with high recurrence risk with close follow-up
PALB2, STK11, PTEN, CDH1	32–60%	• There are no clear recommendations for these mutations, although they carry significant risk • BCS with adjuvant RT may be effective in reducing recurrence risk • Ipsilateral mastectomy ± adjuvant RT would likely reduce recurrence risk. CRRM may be considered depending on shared decision making with patients
MSH	Mixed evidence of elevated risk	• Due to the unclear breast cancer risk, case-by-case shared decision making is most appropriate for these patients
Low-moderate penetrance genes		
CHEK2, BARD1 RAD51, NF1	20–40%	• Further evidence is necessary for clear recommendations in these patients • BCS with adjuvant RT likely effective for reducing recurrence • Insufficient evidence to recommend RRM in these patients due to solely the presence of these mutations
ATM	20–40%	•Radiation exposure maybe associated with increased risk for contralateral breast cancer in women who are carriers of very rare ATM missense variants. However, these variants are not P/LP and a meta-analysis including five studies showed that radiation therapy (with conventional dosing) is not contraindicated in patients with a heterozygous ATM P/LP variant • Insufficient evidence for RRM. Locoregional management based on family history • BCS may be acceptable, although recurrence risk is higher without adjuvant RT

SLNB sentinel lymph node biopsy, *CRRM* contralateral risk reducing mastectomy, *BCS* breast conserving therapy, *RT* radiotherapy, *RRM* risk reducing mastectomy

genome integrity through DNA repair [35–37]. As such mutations in these genes represent significant oncogenic risk, and are the cardinal mutations in hereditary breast cancer — up to 80% of hereditary breast cancers are associated with *BRCA* mutations [38]. Additionally, mutations in these genes cause ovarian, pancreatic, and prostate cancer, underscoring both their broad importance in maintaining DNA integrity and resultant oncogenic risk conferred by these mutations [37]. As individuals with *BRCA1/2* mutations carry a lifetime risk of 60–80%, develop breast cancer at a younger age, and carry a recurrence rate of up to 0.4% per year, risk reduction is a key component of management [39–42]. Breast conserving therapy (BCS) may be an appropriate option for individuals with *BRCA1/2*-associated breast cancer, with post-operative radiotherapy (RT) shown to be effective at reducing the development of recurrent ipsilateral disease [43••, 44]. Further, RT shows no increased toxicity in those with *BRCA1/2* mutations [45, 46].

However, even after BCS and RT, patients with *BRCA1/2* mutations have an increased risk of second cancers in the ipsilateral and contralateral breasts. Due to this increased risk of both a second ipsilateral cancer and a contralateral cancer, bilateral mastectomies are often appropriate options for these patients [43••, 47]. If the diagnosed cancer is not present in the proximity of the nipple, nipple-sparing mastectomies (NSMs) have been shown to provide effective treatment and risk-reduction while also improving cosmetic satisfaction [43••, 48, 49]. Sentinel lymph node biopsy (SLNB) is indicated in the involved ipsilateral breast, but is not routinely indicated in the contralateral risk-reducing mastectomy (CRRM), as the literature demonstrates only between 3 and 6% of CRRMs with SLNB result in the diagnosis of occult carcinoma in the contralateral lymph nodes [40, 43••, 50]. RT in the ipsilateral breast following mastectomy again has been shown to be effective in reducing recurrence risk and is recommended if indicated [47, 51, 52]. Another area of investigation for individuals who do not choose to undergo CRRM is prophylactic RT to the contralateral breast — this has shown effective risk reduction and, importantly, a low rate of the development of radiation-associated malignancies

[53–56]. In patients who undergo prophylactic RT, salvage mastectomy may be an option in the case of recurrence, although further research in this area is needed [57].

Other High Penetrance Genes Associated with Breast Cancer

Although BRCA1/2 mutations are the most common hereditary mutations associated with breast cancer, several other mutations carry a lifetime breast cancer risk of between 35 and 90%. These mutations include *TP53*, partner and localizer of *BRCA2* (*PALB2*), serine/threonine kinase 11 gene (*STK11*), phosphatase and tensin homolog tumor suppressor gene (*PTEN*), and cadherin 1 gene (*CDH1*). Genes encoding microsatellite instability and repair (*MSH/MLH*) mutations also show high penetrance, but their role in breast cancer is less clear. Although a high risk of breast cancer has been demonstrated, these mutations are more rare and have less current evidence regarding the natural history of and effective treatment regimens for cancers associated with these mutations. Thus, there are less clear management recommendations for patients with these mutations, although the body of available literature is growing. Below, we summarize the current evidence for locoregional management recommendations in these patients.

Li-Fraumeni syndrome is associated with mutations in the cancer suppression gene *TP53*, resulting in a lack of functional p53 to mediate DNA repair and cell cycle arrest in the setting of DNA damage. Individuals with LFS carry a lifetime risk of breast cancer of approximately 85% [43••, 58–63]. Individuals with LFS also develop breast cancer at young ages, amplifying the effect of their diagnosis on quality-adjusted life years in these individuals [43••, 58–63]. Similar to those with *BRCA1/2* mutations, risk-reducing mastectomy is commonly offered to these patients. Although studies have not investigated NSMs in the context of LFS, it is reasonable that NSM would be preferred for the same reasons in this population if there is no nipple involvement [43••, 48, 49]. However, an additional consideration for LFS is the risk of RT-associated malignancies. As the gene encoding p53 is mutated, RT-induced DNA damage may accumulate, and individuals have been described to develop additional breast cancers, as well as sarcomas and leukemias, after RT [64, 65]. As such, RT should be considered carefully on a case-by-case basis, and local RT is preferred in cases with high recurrence risk [64, 65].

Although more rare, mutations in *PALB2*, *STK11*, *PTEN*, and *CDH1* mutations are also associated with a high risk of breast cancer. *PALB2* interacts with *BRCA2* to suppress tumor growth, and mutations in this gene thus create a pro-oncogenic environment [66–68]. As such, individuals with these mutations are at high risk for breast cancer, with between a 35–90% cumulative risk of developing breast cancer by age 70 [69, 70]. Additionally, there is evidence that these patients may have a poorer prognosis compared to patients with non-hereditary breast cancer [71]. Mutations in *STK11*, which also encodes for a tumor suppressor, similarly cause a pro-oncogenic environment [72]. Mutations in this gene cause Peutz-Jeghers syndrome, more commonly thought of for its association with mucosal pigmented lesions and GI cancers. It is thought to confer an estimated lifetime breast cancer risk of over 50% [70, 73–77]. Nonfunctional variants of *PTEN* are associated with hamartoma tumor syndromes, of which the most common disorder is Cowden syndrome [78]. *PTEN* mutations also confer an estimated lifetime risk of breast cancer between 60 and 85% [79–81]. Finally, *CDH1* functions as a tumor suppressor, and specifically a suppressor of metastasis and uncontrolled growth, and mutations in this gene are associated with a lifetime risk of developing breast cancer of up to 60% [82–88].

As indicated by the wide range of estimates for the risk of cancer development with each of these mutations, there is insufficient evidence in the current literature supporting universal recommendations for locoregional management in these populations. However, given the high lifetime cancer risk and the relatively younger ages at which patients with these mutations present, risk-reducing mastectomy may be a reasonable treatment for these patients. Adjuvant RT in order to reduce recurrence risk may be an important component of therapy, as well, especially in patients who choose BCS for surgical management. Although RT is potentially effective and the current literature does not support contraindications to RT in these patients, further research regarding the efficacy and toxicity associated with adjuvant RT is warranted to provide appropriate recommendations for its use. Due to the lack of evidence for universal recommendations for locoregional management, it is important to account for patient preference and family history of breast cancer when deciding on treatment regimens.

Finally, *MSH* and *MLH* are genes encoding proteins involved in mismatch repair, with mutations in these genes resulting in accumulating DNA damage and oncogenic transformation. Mutations in this gene are associated with Lynch syndrome, and carry increased risk for colon, endometrial, ovarian, and stomach cancers [89–91]. The risk of breast cancer is less clear, as studies are mixed regarding an elevated risk in these patients compared to the general population [92]. However, recent population-based studies have not showed an increased risk of breast cancer [93, 94]. As such, there is no current evidence or recommendation for CRRM in these patients except for those deemed high-risk due to other factors.

Other Relevant Genes

Along with the high-risk genes described above, several other mutations confer a moderate risk of breast cancer.

These include the ataxia telangiectasia mutation (ATM), checkpoint kinase 2 (*CHEK2*), BRCA1-associated RING domain 1 (*BARD1*), *RAD51*, and neurofibromatosis type 1 (*NF1*), and these carry a lifetime risk of developing breast cancer of approximately 15–40% [93–107].

Physiologically, *ATM* is involved in tumor suppression through cell cycle arrest, with the ATM kinase interacting with other proteins such as p53 and BRCA1 to stop cellular proliferation in the presence of DNA damage [108–110]. Mutations in *ATM* disrupt this function, predisposing patients to a variety of cancers, with the interaction between the ATM kinase and *BRCA1* thought to underlie the risk of breast cancer specifically. Additionally, mutations in this gene are associated with a clinical syndrome involving cerebellar ataxia and dermatologic findings such as telangiectasias [111]. *CHEK2* encodes for a tumor suppressor that is also involved in the physiologic response to DNA damage, and mutations in *CHEK2* have been implicated in Fanconi anemia [96]. *CHEK2* also interacts with *BRCA2*, and mutations predispose patients to breast cancer as well as a variety of other cancers whose prevalence is still being investigated [112–114]. *BARD1* is a related gene encoding for a tumor suppressor that interacts with *BRCA1* mutations, and mutations are associated with breast and ovarian cancer [94, 101, 107, 115]. *RAD51* encodes for an ATPase that is crucial for DNA repair and also interacts with *BRCA1/2*. Mutations in this gene predispose patients to develop breast and ovarian cancer, as well as cancer in other organs [95, 116]. Finally, *NF1* encodes for neurofibromin, which is involved in cellular proliferation. Mutations in this gene result in a well-known systemic syndrome which predisposes the development of numerous peripheral neurofibromas and CNS tumors, as well as a higher likelihood of breast cancer [105, 117].

As with the high-risk mutations described above, there is insufficient evidence for clear recommendations for surgical management in patients with these mutations. However, risk-reducing mastectomy may be a reasonable treatment option, for similar reasons as discussed above. However, the cumulative cancer risk is lower, and thus, breast conservation therapy may have more of a role in individuals with these mutations compared to the high penetrance mutations. Finally, there are some specific considerations that have emerged relating to these genes. For example, patients with *ATM* mutations are known to be more susceptible to radiation toxicity, both with immediate soft tissue complications such as fibrosis and telangiectasias, but also the risk of future malignancy secondary to radiation [118, 119]. Notably, there is some evidence that *ATM* pre-disposes patients to RT-induced malignancy in the contralateral breast, although the literature does not support avoiding RT due to the presence of ATM [120–123]. Additionally, *RAD51* mutations have been associated with a poor prognosis, although further research is needed [95]. These patients also require significant screening, and may benefit from being followed at a hereditary syndrome clinic if available to them.

Gene Expression Assays

The Role for Expanded Use of Gene Assays

In addition to hereditary mutations associated with breast cancer that are routinely tested for, gene expression assays provide an additional tool for determining appropriate treatment for patients diagnosed with breast cancer. Specifically, the use of gene assays has been shown to be an effective tool to identify individuals diagnosed with breast cancer who would benefit from adjuvant systemic therapies [124–129]. Currently, NCCN guidelines recommend the incorporation of 21-gene expression assays within clinical decision-making guidelines for adjuvant systemic therapy [130••]. In addition, there are other commercially available tests that are becoming more accessible that show similar efficacy, although with more limited research [130••, 131–135]. The clinical uptake of these gene assays has been significant, and retrospective studies have further established their improvement of clinical outcomes [136•, 137•, 138, 139].

Although effective and routinely used to identify individuals who would benefit from systemic adjuvant therapy, these tests are not used for decision-making regarding locoregional management. However, there is evidence supporting its potential utility in such a role [140]. Early attempts at utilizing gene expression profiling of breast cancer did successfully show prognostic value in terms of survival, but its role in locoregional recurrence and management decision-making has yet to be fully elucidated [141–143]. Another early study showed that gene expression profiling could accurately predict locoregional recurrence of breast cancer [144]. These studies were done utilizing previously available gene assays, but more recent evidence supports similar findings using more contemporary gene assays, particularly the aforementioned 21-gene assay that is incorporated into NCCN guidelines. In node-negative individuals that were hormone receptor-positive, the gene assay was shown to accurately predict locoregional cancer recurrence [145, 146]. This gene assay was shown to predict recurrence in node-positive disease, as well as in studies that include both node-positive and -negative disease [147••, 148, 149••, 150]. Finally, in individuals status post adjuvant systemic treatment, the use of a gene assay was similarly able to predict future locoregional recurrence risk [151].

This finding has potentially significant implications on management. First, those found to have a high rate of locoregional recurrence based on gene expression profiling would likely benefit from adjuvant RT after BCS to reduce future risk of recurrence. Additionally, patients may

opt for mastectomy given the higher chance of recurrence. The growing use of these assays and their incorporation in clinical decision-making regarding systemic therapy represents an opportunity to investigate their utility in identifying appropriate locoregional treatment options. Future research in this area may further improve management decisions and precision.

Conclusion

Great advances have been made in defining appropriate management and counseling for patients with breast cancer and who have hereditary genetic mutations. With the exception of *ATM* mutations, breast conserving surgery and radiation or mastectomy are effective management regimens for these individuals. Contralateral risk reducing mastectomy is also often appropriate, in conjunction with patient counseling and shared decision-making. Furthermore, gene expression assays may provide an additional tool for determining appropriate locoregional management options for patients in the future, and specifically may identify those in which radiotherapy would be particularly beneficial.

Future Directions

The current literature also elucidates several promising areas of future study. First, research into appropriate modes of locoregional management of breast cancer in individuals with hereditary mutations other than *BRCA1/2* would establish appropriate recommendations and guidelines, and thus potentially improve outcomes in these individuals. Further defining the clinical significance of more rare mutations and potential gene–gene interactions in cases with multiple co-occurring mutations remains an area of potential investigation. Additionally, the current literature also shows existing disparities in locoregional treatment of breast cancer as well as the availability of gene assays to guide treatment. Identifying the sources of these socioeconomic and racial disparities would allow for wider access to guideline-based breast cancer care and targeted therapy [135, 139, 152, 153]. Finally, continued study of the utility of gene expression assays for determining individuals who would most benefit from radiation therapy may solidify its promise and role in routine breast cancer management.

Declarations

Conflict of Interest The authors declare no competing interests.

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