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Multigenic panels in breast cancer: Clinical utility and management of patients with pathogenic variants other than *BRCA1/2*

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ABSTRACT

Multigene panels can analyze high and moderate/intermediate penetrance genes that predispose to breast cancer (BC), providing an opportunity to identify at-risk individuals within affected families. However, considering the complexity of different pathogenic variants and correlated clinical manifestations, a multidisciplinary team is needed to effectively manage BC. A classification of pathogenic variants included in multigene panels was presented in this narrative review to evaluate their clinical utility in BC. Clinical management was discussed for each category and focused on BC, including available evidence regarding the multidisciplinary and integrated management of patients with BC. The integration of both genetic testing and counseling is required for customized decisions in therapeutic strategies and preventative initiatives, as well as for a defined multidisciplinary approach, considering the continuous evolution of guidelines and research in the field.

Abbreviations: BC, Breast cancer; CP, critical pathway; ER, Estrogen Receptor; MGPT, Multigene Panel Test; MMR, mismatch repair; MTB, molecular tumor board; NGS, next-generation sequencing; CPG, cancer predisposing gene; PV, pathogenic variant; RRM, risk-reducing mastectomy; TB, Tumor board; VUS, variants of uncertain significance.

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1. Introduction

About 5–10 % of breast cancers (BCs) are believed to be hereditary (Hu et al. 2021). The risk of developing BC associated with the presence of germline disease-causing variants depends on the gene involved. Conventionally, two categories of cancer predisposing genes (CPGs) are recognized, the so-called high and moderate/intermediate penetrance genes, which, for BC, entail lifetime risks >40 % and 20–40 %, respectively (Easton et al., 2015; Spurdle et al., 2019). *BRCA1* and *BRCA2* are well-known high-penetrance genes that predispose to BC and ovarian cancer, as well as to other malignancies, namely prostate and pancreatic cancer (Sheikh et al., 2015; Hawsawi et al., 2019). However, variants in *BRCA1* and *BRCA2* only explain about 25 % of suspected hereditary/familial cases (Wang et al., 2018). Additional genes, including several involved in DNA repair mechanisms, such as *ATM, TP53, PALB2, CHEK2, RAD51C,* and *RAD51D*, confer variable increased risk for BC and other cancers (Concolino et al., 2019).

Advancements in DNA sequencing technologies, particularly the widespread adoption of next-generation sequencing (NGS)-based approaches, have facilitated the study of the molecular bases of human diseases. Multigene panels (MGPs) that simultaneously and rapidly analyze CPGs have shed further light on the contribution of individual genes to hereditary cancer predisposition, expanding opportunities to identify at-risk individuals within affected families (Fountzilas and Kaklamani, 2018; Catana et al., 2019; Nunziato et al., 2018; D'Argenio et al., 2015). In addition to the increased discovery rate of clinically significant variants (i.e., likely pathogenic or pathogenic variants - hereafter collectively defined as "pathogenic variants" [PVs]) (Plon et al., 2008; Richards et al., 2015), multigene testing has also increased the detection of DNA variations without a clear clinical significance (variants of uncertain significance [VUS]). The frequency of MGP tests reporting the detection of VUS ranges from 6.7 % to 41.7 % and is positively correlated with the number of genes tested (Doherty et al., 2015; Tung et al., 2015).

Following the increasing clinical use of MGPs, the National Comprehensive Cancer Network (NCCN) guidelines for hereditary BC have been updated to include additional CPGs beyond *BRCA1* and *BRCA2*; each gene is classified according to very strong, strong or limited evidence of increased risk of specific cancer types (Mc Alarnen et al., 2021).

The genes included in MGPs used for BC can be divided into the following categories according to the magnitude of risk conferred, the organs at risk, the frequency of detected PVs, the associated clinical recommendations, and the extent and significance of available scientific evidence:

A. *High-risk BC CPGs*, not associated with specific manifestations, for which clinical recommendations and strong supporting evidence are available (i.e., *BRCA1, BRCA2, PALB2*);
B. *Other high-risk BC CPGs*, involved in rare hereditary syndromes associated with specific phenotypic manifestations, for which clinical recommendations and strong supporting evidence are available (i.e., *TP53, PTEN, STK11, CDH1*);
C. *Well-established non-BC CPGs*, such as the mismatch repair (MMR) genes involved in Lynch syndrome, do not confer a significant BC risk;
D. *Moderate-risk CPGs*, for which clinical recommendations and supporting evidence are available (i.e., *ATM, CHEK2, BARD1, BRIP1, NF1, RAD51C, RAD51D*);
E. *Candidate moderate-risk CPGs* for which insufficient evidence is available (i.e., *FANCM* and other genes involved in homologous recombination repair or additional genes involved in other pathways). This category also includes genes previously established as moderate-risk CPGs but have not been subsequently confirmed by scientific evidence (i.e., *NBN*).

Overall, categories A to D include genes that are deemed clinically useful. However, the degree of utility varies across these groups and among specific genes within the same group.

Different sets of recommendations on the use of MGPs for BC predisposition have been published (reviewed in Tung et al., 2024). The content of genes considered for inclusion is variable, ranging from only *BRCA1* and *BRCA2* (Xie and Wang, 2021) to > 10 (NCCN 2024; Taylor et al., 2018; Sessa et al., 2023). The expert working group of the American Society of Clinical Oncology has identified two sets of BC genes with different penetrance values and strength of recommendations: the high-risk group genes should always be offered, while the moderate-risk ones are less strongly recommended (Tung et al., 2024). In addition, it is suggested to consider the use of a broader panel when this entails potential clinical benefits.

Clinically, it is noteworthy that a single PV can be associated with different clinical manifestations, while, at the same time, similar phenotypes can be caused by different PVs and genes. A multidisciplinary team should address this complexity to warrant effective management of hereditary cancer predisposition, a rapidly evolving area. In recent years, clinical pathway models have been proposed for patients with BC with PVs and VUS, involving initial genetic testing with the support of an oncologist and a clinical genetic consultant [Eccles 2015]. A close and constant working relationship between oncologists and geneticists through regular multidisciplinary team meetings is necessary to optimize the management of affected patients and their family members. This is especially relevant for integrating tumor (TB) and molecular tumor (MTB) assessment boards into BC care networks, aiming to link hospital and community centers into timely and efficient care pathways.

This narrative review evaluates the clinical utility of MGPs in BC. To this end, it examines the available evidence on the multidisciplinary and integrated management of patients with BC with PVs other than *BRCA1/2*.

2. Methods

Two electronic databases (PubMed and Scopus) were interrogated to perform the literature search, using the following keyword combinations: breast cancer AND variant of uncertain significance, breast cancer AND *BRCA1/2*, next-generation sequencing AND breast cancer, multigene panel test AND breast cancer. The search was concluded in July 2023. No restriction was applied to publication dates. After eliminating duplicate results, the initial screening was carried out by three authors (AF, SD and MG) based on the title and abstract of the papers. The following inclusion criteria were applied: original research articles, reviews, and book chapters written in English and investigating BC, gene variants, and their implications in clinical practice. All eligible papers were subjected to a full-text review. A separate consensus of the other authors resolved any disagreement in the selection phase.

3. Clinical utility of multigenic panels in breast cancer

For each of the categories mentioned in the Introduction, we discuss the clinical utility and the proposed clinical management of BC (e.g., mammography, MRI screening, risk-reducing mastectomy [RRM]). Generally, testing for a given gene may be considered clinically useful if changes in clinical practice are advised for PV carriers versus either non-carriers or individuals who have not been tested.

Category A: Clinical validity, utility and actionability are well established for the three genes (*BRCA1, BRCA2, PALB2*) in this group. All of them entail high (>40 %) absolute risks of BC, and specific surveillance advice is given to carriers (Yadav et al. 2023; Fackenthal and Olopade, 2007; Antoniou et al. 2014; Carter, 2001; Uyei et al. 2006).

Category B: Overall, *TP53, PTEN, STK11,* and *CDH1* are associated with similar BC risk levels and management advice as category A [Foretovà et al. 2019]. However, there are important differences in the frequency of involvement and clinical characteristics. Their PVs cause

rare/very rare hereditary conditions, and affected patients present with phenotypic manifestations that usually prompt the diagnosis before BC development or based on specific histological characteristics of BC (i.e., lobular carcinoma for *CDH1*) (Blondeaux et al., 2023; Apostolou and Fostira, 2013; Valdez et al. 2017; Milani et al. 2023). Given the rarity of these conditions and the availability of specific criteria for clinical diagnosis, their inclusion in a diagnostic panel may provide, at most, a marginal increase in sensitivity.

Category C: Nowadays, testing for CPGs is performed in two main clinical settings: for targeted prevention in individuals at high risk or to guide therapeutic choices (Rahman, 2014). In the latter case, the indications for genetic, germline, or somatic testing depend on the patient's clinical pathological characteristics and are unrelated to the criteria adopted for cancer predisposition testing. In the former setting, it is now common practice to use CPG diagnostic panels that cover a wide array of cancer predisposition syndromes, not limited to the clinical phenotype for which the test has been requested. A PV in a gene unknown to be associated with an increased BC risk found in an individual tested for suspected hereditary BC may be considered a secondary finding (Miller et al., 2023). In this case, the relationship to the clinical phenotype is unclear. It is possible that occasionally, a gene not significantly associated with BC susceptibility, such as the MMR genes *MSH2, MLH1,* and *MSH6*, may be involved in breast tumorigenesis in some individuals, but conclusive evidence supporting a causal link is difficult to obtain (Caluseriu et al., 2001; Stoll et al., 2020; Harkness et al., 2015). Therefore, in Lynch syndrome, the risk of BC and related surveillance should be empirically established based on family history. On the other hand, another important issue is estimating the effective risk magnitude for Lynch syndrome characteristic cancers. In such cases, family history should be enquired to ascertain whether it presents features indicative of Lynch syndrome. The lack of a suggestive phenotype could be due to reduced penetrance of specific PVs and/or modifier factors shared by pedigree members. In principle, this could be a reason to advise less intensive surveillance. However, studies are needed to determine the reasons underlying the different phenotypic presentations of MMR genes (Turnbull et al., 2018). Thus, the standard recommendations are currently provided to individuals at high risk of cancer identified incidentally following expanded panel testing. This means that individuals with an MMR gene PV detected upon testing for suspected hereditary BC should be advised to undergo Lynch syndrome-specific surveillance or, conversely, that carriers of *BRCA1* or *BRCA2* PVs identified in a Lynch syndrome candidate family should be provided with the appropriate recommendations for BC and ovarian cancer risk reduction even in the absence of a BRCA phenotype. Similar considerations apply to other CPGs in this category.

Category D: PVs in *ATM, CHEK2, BARD1, NF1, RAD51C,* and *RAD51D* are characterized by lower penetrance values for BC, limited evidence on the effectiveness of surveillance, incomplete knowledge of the risks associated with different tumor types, the potential role of family history of cancer and genetic variants in low-risk genes in determining the magnitude of risk, and the not-rare occurrence of phenocopies in pedigrees (Yadav et al. 2023; Graffeo et al. 2022; Vysotskaia et al. 2020). Since clinical trials evaluating the effects of different interventions would require the recruitment of a great number of patients, preventative advice is mostly based on expert opinion or data obtained in other settings, such as from carriers of high-risk PVs in *BRCA1* or *BRCA2*.

This group also includes the *NF1* gene, whose PVs cause a fully penetrant neurocutaneous phenotype that, similarly to the syndromes mentioned in category B, is usually diagnosed before the BC diagnosis in these patients.

Category E: This includes a potentially large number of genes that have been considered candidates for BC predisposition because of their biological function and/or based on the results of epidemiological studies. Representative examples are *NBN, MRE11,* and *RAD50*, which code for the components of the double-strand break sensor complex (Elkholi et al., 2021; Couch et al., 2017), and other genes involved in double-strand break repair, such as *ABRAXAS1*, which encodes a BRCA1 interactor, or other DNA repair genes, such as *FANCM*, a mediator of the stalled replication fork sensor (Panday et al., 2021). For these genes, evidence of clinical utility is insufficient because of the relatively low magnitude of risk (Peterlongo et al., 2015; Figlioli et al., 2023), and the association with cancer risk has often not been confirmed. Despite the lack of clinical utility, variants in these genes are often mentioned in panel test reports.

Some of the genes, namely *NBN* and *RAD50*, belonging to this category were previously indicated as potential moderate risk factors for BC. However, additional data have shown that there is insufficient evidence for association. Extensive datasets have been accrued for these two genes on specific founder variants, *NBN* c.657del5 and *RAD50* c.687delT. The increased risk may apply to specific populations but has not been confirmed in other ethnic groups. *NBN* is included in several MGPs due to both its role in double-strand break repair and the evidence of an association between the common c.657del5 PV and BC risk (Zhang et al., 2013). However, these findings may not apply to other variants of the same gene and have not been confirmed by population studies (Hu et al., 2021). When the *NBN* gene was initially considered in the NCCN guidelines for hereditary breast/ovarian cancer, specific breast surveillance advice, including MRI, was provided for female PV heterozygotes (Daly et al., 2021). However, additional data did not support *NBN* actionability for BC risk, so these surveillance recommendations have been removed from the NCCN guidelines since 2021 [NCCN, 2023]. This recommendation change is a paradigm of the difficulties associated with establishing correct clinical advice for intermediate penetrance genes. Similar considerations apply to the Finnish *RAD50* c.687delT variant (Heikkinen et al., 2006; Uhrhammer et al., 2009; Fan et al., 2018).

4. Clinical management related to BC risk

A summary of the evidence on the clinical utility and management of MGPs according to the above-described gene categories is provided in Table 1.

The above-defined categories pertain essentially to the preventative setting, although there is considerable overlap between CPGs tested for cancer predisposition and for predicting treatment response. In the preventive setting, the ClinGen Resource has devised a semiquantitative approach aimed at defining, for each gene, the clinical actionability for different types of interventions (e.g., for CPGs, intensive surveillance, or prophylactic surgery) and for different clinical manifestations (e.g., breast versus ovarian or other cancers) (Hunter et al., 2016). No conclusive data are available on the role of chemoprevention using tamoxifen/raloxifene and aromatase inhibitors for *BRCA1/2* variant carriers, while no data are reported for other genes (King et al., 2001; Nemati Shafaee et al., 2015). The severity of clinical manifestations, disease-specific penetrance, effectiveness, risks associated with the proposed intervention, and the level of scientific evidence, which ranges from substantial to poor/conflicting, are considered.

4.1. *PALB2*

Following initial uncertainty about risk effects, *PALB2* has been proven to be a high-penetrance BC gene, also causing a moderate increase in the risk of ovarian and pancreatic carcinoma (Yang et al., 2020). The absolute risk of BC associated with *PALB2* PVs is in the range of 41–60 % (Yang et al., 2020 NCCN last version). For *PALB2* PV carriers, recent data revealed an association with estrogen receptor (ER)-negative BC (Dorling et al., 2021; Dorling NEJM et al. 2021). In addition, *PALB2* PV carriers were found to have a significantly increased risk of contralateral BC only when the first cancer was ER- and premenopausal (Yadav et al., 2023). For these patients, an annual mammography and breast MRI screening are recommended alternating once every 6 months, starting at age 30 years. Screening and/or risk-reducing surgery should be discussed and individualized based on

Table 1
CPGs included in MGPs: clinical manifestations, BC risk, and recommendations for clinical management of BC.

Category	Risk class	Genes	Absolute risk	Associated conditions	Recommendations NCCN v 2.2024 and ESMO 2023 for BC preventative management
A	High risk	*BRCA1/2*	>60 %	– Breast, ovarian, pancreatic, prostate cancer	– Annual mammography and breast MRI with contrast screening starting at age 30 – Discuss the option of RRM
		PALB2	41–60 %	– Breast, ovarian, and pancreatic cancer	– Annual mammography and breast MRI with contrast from age 30 – Discuss the option of a risk-reduction strategy
B	High risk	*CDH1*	41–60 %	– Breast cancer, lobular phenotype, and gastric cancer	– Annual mammography and consider breast MRI with contrast starting at age 30 – Discuss the option of a risk-reduction strategy
		PTEN	40–60 %	– Multiple benign and malignant manifestations, including breast, renal, and endometrial cancer, – Mucocutaneous hamartomas and other dermatological lesions, melanoma, macrocephaly, benign thyroid disease, gastrointestinal polyps	– Annual mammography and breast MRI with contrast screening starting at age 35 or 10 before the earliest known breast cancer in the family – Discuss the option of a risk-reduction strategy
		STK11	32–54 %	– Breast, pancreatic, and rare gynecological cancers – Mucocutaneous pigmentation and hamartomatous gastrointestinal polyps	– Annual mammography and breast MRI with contrast starting at age 30 – Discuss the option of a risk-reduction strategy
		TP53	>60 %	– Sarcomas, adrenal carcinomas, brain tumors, leukemias, BC, and other cancers	– Annual breast MRI with contrast and mammography – Discuss the option of a risk-reduction strategy
C	Established CPGs are not known to be associated with higher BC risk	*MLH1, MSH2/6 PMS2*	<15 %	– Colorectal and endometrial carcinoma, other cancers	– No specific recommendations
D	Moderate risk	*RAD51C/D*	17–30 %	– Breast and ovarian cancer	– Annual mammography and consider breast MRI with contrast starting at age 40
		ATM	20–30 %	– Breast, ovarian, pancreatic, and prostate cancers	– Annual mammography from age 40 and consider breast MRI with contrast starting at age 30–35
		CHEK2	20–40 %	– Breast cancer, possibly other cancers	– Annual mammography from age 40 and consider breast MRI with contrast starting at age 30–35
		BARD1	17–30 %	– Breast cancer	– Annual mammography and consider breast MRI with contrast starting at age 40
		NF1	20–40 %	– Nervous system tumors (especially malignant peripheral nerve sheath tumors), gastrointestinal stromal tumors and breast cancer	– Annual mammography starting at age 30 and consider breast MRI with contrast from ages 30–50

family history (Tung et al., 2016).

4.2. *CDH1*

CDH1 was initially recognized as the gene involved in hereditary diffuse gastric cancer (Guilford et al., 1998). It became apparent that hereditary diffuse gastric cancer is also characterized by a high risk of BC, particularly lobular histotype. Indeed, lobular BC was the neoplasm showing the greatest association with the presence of *CDH1* PVs in a large European dataset, and it was the only tumor recorded in 7 % of the families having only lobular BC (Garcia-Pelaez et al. 2023). The risk of BC among women is 55 % by the age of 80 years (Roberts et al., 2019). The International Gastric Cancer Linkage Consortium guidelines recommend annual breast MRI with contrast beginning at the age of 30 and continuing at least until the age of 50 years (Blair et al., 2020). Annual mammography is also recommended from the age of 40 years and should be considered from the age 35 years, but it should not be the only imaging screening method unless there are contraindications to MRI; in the latter case, a breast ultrasound should be performed. RRM can be discussed by taking into account family history.

4.3. *PTEN*

PTEN hamartoma tumor syndrome, caused by PVs in the tumor suppressor *PTEN* gene, is a pleiotropic condition with multiple benign and malignant manifestations, including mucocutaneous hamartomas and other dermatological lesions, macrocephaly, and benign thyroid and/or breast disease (Blumenthal and Dennis, 2008). Carriers of *PTEN* PVs have a lifetime risk of developing BC between 54 % and 78 %, with a more significant increase between the ages of 30 and 40 than in the general population and median age at diagnosis of 42–43 years (Hendricks et al., 2021; Hendricks et al. 2023). The guidelines developed by the European Reference Network on Genetic Tumor Risk Syndromes recommend annual breast MRI from the age of 30 years, with mammograms every 2 years from age 40 years (Tischkowitz et al. 2020). Although data on risk-reducing surgery in women or patients with BC with Cowden syndrome are not available, the option of bilateral mastectomy should be considered, taking into account family history. Specific surveillance is also recommended for other organs at increased risk of cancers, namely endometrial, renal, thyroid and colorectal carcinoma.

4.4. *STK11 (Peutz-Jeghers syndrome)*

Peutz-Jeghers syndrome is a very rare condition caused by PVs in the *STK11* gene. It is usually diagnosed during childhood or adolescence by the presence of characteristic pigmentation and hamartomatous gastrointestinal polyps that bleed and/or cause bowel intussusception (Tacheci et al., 2021). The risk of BC, estimated on small cohorts, ranges from 19 % to 54 % (Wagner et al. 2021). In *STK11* mutation carriers or patients with BC, an annual breast contrast MRI screening should be recommended from the age of 25–30 years, combined with mammography from the age of 30 years (Wagner et al. 2021).

4.5. TP53 (Li Fraumeni syndrome; heritable TP53-related cancer syndrome)

While somatic *TP53* mutations are detected in about 40–50 % of cancers of different types, germline alterations are associated with Li-Fraumeni syndrome, recently redefined as a group of "heritable TP53-related cancer syndromes" by the European Reference Network on Genetic Tumor Risk Syndromes because of the broadening of the phenotypic spectrum from the original descriptions (Frebourg, 2020). Subjects with this syndrome present a significantly increased risk of developing not only BC at a young age but also a variety of other neoplasms. No specific non-malignant manifestations are associated with the condition. Personal and family history of cancer are the two most important clinical elements for diagnosis (Miranda Alcalde et al., 2021; Bougeard et al., 2015]. The tumor spectrum is very wide, but specific "core" cancers have been recognized (Table 2). Germline *TP53* testing is advised for patients fulfilling the so-called Chompret Criteria, for children with specific rare tumors, and for individuals who develop a second primary tumor after treatment for a previous cancer before the age of 46 years (Table 2).

BC is the most common cancer in female carriers of *TP53* PVs, with an estimated cumulative incidence between 38 % and >60 % and very high risk at young ages, including <25 years (Mai et al. 2016; Shin et al. 2020; NCCN vers. 2.2024). BCs in carriers of the *TP53* variant are associated with HER2 positivity (Masciari et al., 2012; Wilson et al., 2010).

Although only a few studies have evaluated the effects of radiotherapy, because of evidence of increased risk of secondary cancers, it is generally advised to avoid radiation therapy whenever possible (Hendrickson et al., 2024). A retrospective study investigating a cohort of 322 affected patients concluded that the incidence of secondary tumors in a previous radiation field was 30 %, with an average time to diagnosis of 10.7 years (Bougeard et al., 2015). Clear guidelines on the use of radiation therapy in this population are not yet available. However, patients with cancer predisposition syndromes, such as the Li Fraumeni syndrome (LFS), have a higher risk of developing radio-induced malignancies, such as BC, and also colon cancer, thyroid cancer, and especially sarcomas, than the general population (Heymann et al., 2010; Hendrickson et al., 2024; Le AN 2020]. Therefore, it is important to carefully consider the risks and benefits for each patient. Although there are currently non-specific indications for the choice of chemotherapeutic agents, clinical and experimental data suggest the role of genotoxic agents in the development of secondary cancers (Y. Zerdoumi et al. 2015; Kasper et al., 2018). Screening is essential to prevent relapse of malignancy or second cancer and should be carried out by an experienced multidisciplinary healthcare team; any abnormal symptom should be observed quickly to intervene promptly.

In females, breast screening includes an annual breast MRI starting from the age of 20 years, while mammography should be considered from the age of 30 years (Frebourg, 2020; NCCN). In addition, the option of prophylactic mastectomy should be discussed with those at risk. The screening program is complex and includes whole-body MRI, and, depending on the type of PV and family history, may begin in pediatric age or adolescents/young adults.

Carriers of *TP53* PVs should be educated about a healthy lifestyle; avoiding tobacco and alcohol and minimizing exposure to other suspected carcinogens are strongly recommended, and a balanced weight should be maintained (Pantaleao 2020).

Table 2
Genetic Tumor Risk Syndrome clinical criteria for germline *TP53* testing.

Patients fulfilling the Chompret Criteria	For familial cases: proband with a *TP53* core tumor (breast cancer, soft-tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma) before age 46 AND at least one first- or second-degree relative with a core tumor before age 56 Multiple primitive tumors: proband with multiple tumors, including two *TP53* core tumors, the first of which occurred before age 46, regardless of family history Rare tumors: patients with adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, regardless of family history Very early-onset breast cancer: breast cancer before age 31, regardless of family history
Children	Hypodiploid acute lymphoblastic leukemia Unexplained sonic hedgehog-driven medulloblastoma Jaw osteosarcoma
Other patients	Patients who develop a second primary tumor within the radiotherapy field of a first core *TP53* tumor diagnosed before age 46

Adapted from Frebourg et al. 2020. Published Open Access under a Creative Commons Attribution 4.0 licence.

4.6. ATM

Biallelic PVs of the *ATM* gene cause ataxia-telangiectasia (AT), a rare disorder affecting the central nervous and immune systems with increased cancer risks, while carriers of monoallelic *ATM* PVs are susceptible to the development of malignancies. In females, the cumulative lifetime risk of developing BC is between 20 % and 40 % (6 % until the age of 49 years) (Tung et al., 2016). (Daly et al., 2023; Renwick et al., 2006). Female *ATM* carriers were found to be more likely to develop ER-positive BC than ER-negative BC in two large cohort studies (Dorling et al., 2021; Hu et al., 2021]. The likelihood of developing a second primary BC is unclear (Manfield et al., 2017; Reiner et al., 2020; Morra et al. 2023; Yaddav et al., 2023).

In a retrospective analysis of 443 *BRCA1/2*-negative familial patients with BC and 521 unaffected controls, patients with familial BC were more likely to have *ATM* PVs than the control group (12 versus two carriers, respectively) [Renwick 2006]. Families of patients with AT, especially mothers who are obligate carriers of children affected with AT, should be informed of the increased cancer risks and potential screening options.

Given the evidence of a moderately elevated lifetime risk of BC, female carriers of monoallelic *ATM* PVs should be offered annual mammography with tomography at the age of 40 years and annual MRI from the age of 30–35 years [NCCN 2024]. Given the increased absolute risk of BC, up to 69 %, brought about by the specific PV c.7271 T>G, surveillance can begin with a breast MRI at the age of 25 years and annual mammograms from 30 years for carriers of this variant (van Os et al., 2016). Although there is insufficient risk to warrant RRM, this option should be considered for carriers with a worrisome family and personal BC history. [NCCN 2024]. Two large prospective trials provided no evidence of clinically relevant increased risk of contralateral BC in monoallelic *ATM* carriers [Morra et al. 2023; Yadav 2023].

As a general rule, which also applies to other moderate-penetrance genes, breast, and cancer overall, surveillance recommendations may need to be adjusted based on genotype and family history (van Os et al., 2016).

For cancer patients who are *ATM* PV carriers and require radiation therapy or chemotherapy, the therapeutic indication should not be changed. *ATM* heterozygotes are less vulnerable to ionizing radiation and chemotherapy drugs that cause DNA double-strand breaks (Bernstein et al., 2010). Preliminary data from an observational trial of 91 carriers of *ATM* PVs or VUS undergoing radiation therapy for BC did not indicate high rates of harmful consequences [Leslie 2019]. In general, *ATM* heterozygotes with cancer should be treated with the "best" standard therapies for their specific malignancy without withholding radiotherapy when necessary because the clinical impact of radiation exposure is not well understood (van Os et al., 2016).

4.7. CHEK2

CHEK2 is considered a moderate-penetrance BC gene, and there is evidence of association with other cancers, namely prostate and possibly thyroid, kidney, and colorectal carcinoma [Hanson et al. 2023]. *CHEK2* germline PVs are common in the population, and cancer risk is influenced by several factors, including variant type, family history, and, possibly, genetic and environmental modifiers. As a general rule, truncating PVs (i.e., nonsense, frameshift, and some splice site variants) confer a relative risk >2 and thus warrant specific preventative advice. On the other hand, the effects of most missense variants are either below the risk threshold for clinical actionability, as in the case of common p.(Ile157Thr) and p.(Ser482Phe) variants, or undetermined. A notable exception is the p.(Arg117Gly) variant, which is associated with a BC risk similar to that conferred by truncating variants [Hanson et al. 2023]. The BC lifetime risk for carriers of monoallelic PVs ranges from 17 % to 40 % and depends on family history (Cybulski et al., 2009; Dorlin et al., 2021; Hu et al. 2021]. The increased risk is greatest for women <40 years and for ER-positive BC (Breast Cancer Association Consortium, 2021; Hu et al. 2021). Individuals with biallelic *CHEK2* PVs have a higher risk of BC and other cancers than monoallelic carriers [Hinic et al., manuscript submitted]. Breast surveillance should be tailored according to genotype. For carriers of truncating PVs and possibly the p.(Arg117Gly) missense variant, annual mammograms should be started at least from the age of 40 years, and breast MRI should be considered from the same age [Hanson 2023; NCCN Breast guidelines 02–2024]. No specific preventative strategy should be proposed for other monoallelic missense PVs, and surveillance should be based on personalized assessment, including family history. Data on the benefits of RRM are unavailable; this procedure may be considered based on family history.

4.8. RAD51C and RAD51D

The BRCA1/2 pathway involves the RAD51 paralogs RAD51 paralog C (RAD51C) and RAD51 paralog D (RAD51D). *RAD51C* and *RAD51D* PVs are uncommon and raise the risk of BC, particularly ER-negative, by 10–20 % (Dorling et al., 2021; Hu et al., 2021). They also increase the risk of ovarian cancer [Yang Song et al. 2020].

Female carriers of PVs in RAD51 paralogs should be offered annual mammograms and the option of undergoing breast MRI from the age of 40 years. Although there is inadequate evidence to consistently advise RRM, it may be reasonable to consider it for those carriers who have a positive family history or other risk factors (such as an atypical gland or a diagnosis of BC).

4.9. BARD1

BARD1 germline PVs are significantly associated with BC, especially triple negative, and confer an estimated lifetime risk of 17–30 % (Couch et al., 2017; Kurian et al., 2017; Thompson et al., 2016; Webere-Lassalle et al., 2019; Suszynska et al., 2019; Hu et al., 2020; Slavin et al., 2017, Shimelis et al., 2018, Dorling et al. 2021; Hu et al. 2021; NCCN BOP guidelines 02.2024]. NCCN recommends annual mammograms and consideration of breast MRI with and without contrast starting at the age of 40 years [[NCCN BOP 2.2024]. However, further data need to be accrued to determine the most appropriate age to begin surveillance and its frequency.

4.10. NF1 (type 1 neurofibromatosis)

PVs of *NF1* are associated with an increased risk of nervous system tumors (especially malignant peripheral nerve sheath tumors), gastrointestinal stromal tumors, and BC (Longo et al., 2018). Annual mammography, possibly combined with breast MRI, is suggested between 30 and 50 years of age (Weber-Lassalle et al., 2019). After the age of 50 years, BC risk in women with *NF1* PVs becomes similar to that of the general population. Therefore, breast MRI could be discontinued (Suarez-Kelly et al., 2019), while mammography can be performed further. Data on the benefits of RRM are unavailable; this procedure may be considered based on family history.

4.11. Other genes

Although BC is occasionally reported in carriers of MMR gene PVs, it is not considered a tumor associated with Lynch syndrome. Recently, an association with truncating variants in *MSH6* was observed in a large prospective study (Dorling et al., 2021; Dorling, 2021]. However, the clinical significance of this finding has yet to be established. Therefore, breast surveillance in Lynch syndrome should be based on family history.

Similar considerations apply to the genes in category E, as the association with BC has not been confirmed or is currently unclear. Theoretically, this approach should also be applied to common damaging founder variants in some of these genes, such as the Slavic *NBN* 675del5, although population-specific guidelines elaborated based on studies analyzing risk levels for the ethnic groups involved, if available, can be applied (Rusak et al., 2019).

5. Variants of uncertain significance

VUS are typically missense, silent, or intronic/noncoding changes or in-frame deletions and insertions, whose effect on protein function is often uncertain. Because of the complex process involved and the lack of standardized criteria, interpretation of the potential pathogenicity of VUS presents some difficulties, and discrepancies among laboratory reports are occasionally noted. The frequency of VUS varies worldwide, depending on the criteria used for testing and population ancestry. Researchers have reported a frequency of VUS of 21 % in African–Americans, 5–6 % in people of European ancestry in the USA, and 15 % in European laboratories (Kim et al., 2021). When a VUS is identified, preventative clinical management depends entirely on a family history of cancer and assessment of other risk factors. Misclassification of a variant as likely pathogenic can lead to “over-management”. Conversely, significant consequences of variants under classification can occur with interventions that are not tailored to the true level of risk (Garrett et al., 2021). Limited studies are available in the literature investigating the impact of *BRCA* VUS on clinical decision-making. Some of these have reported comparable mastectomy rates between patients with *BRCA* wild type and *BRCA* VUS (Culver et al., 2013). Other authors have highlighted intermediate rates, higher than in *BRCA* wild-type and lower than in *BRCA*-positive patients (Welsh et al., 2017). However, it is challenging to understand whether prophylactic surgery has been adopted, taking into account the combination of VUS identification with other factors, e.g., family history or psychological distress. The widespread use of NGS high-throughput technologies has greatly increased the number of MGP tests, also leading to the identification of an increasing number of VUS (Lucci-Cordisco at al. 2022). However, a VUS cannot be used for clinical management of carriers or to offer cascade testing to individuals at risk in the family. Therefore, efforts should be encouraged to systematically review the interpretation of a VUS by reporting laboratories in order to provide optimal advice to all carriers of the BC CPG variant.

6. The available tools for the pathway of PVs and VUS in BC

BC is a complex disease with several assessments to be carried out, such as somatic and germline molecular investigation and evaluation and subsequent therapeutic and preventative indications. Therefore, it is essential that the care of patients with BC moves to integrating MTB and TB to maximize the beneficial effects of multidisciplinarity. A well-managed care network is necessary to ensure proximity, equity,

continuity, and homogeneity of healthcare delivery and proactively accompany the patient in the different phases of the clinical pathway. This should identify the connections between healthcare providers by defining their operating rules, monitoring system, quality and safety requirements for processes and care pathways, qualification of professionals involved, and approaches for citizen involvement [www.quotidianosanita.it/allegati/allegato1675069692.pdf]. Further clinical impact may arise from transforming critical pathways (CP) into dynamic tools integrating a patient-centered approach with a personalized perspective in compliance with a shared decision-making framework (Angioletti et al., 2022). Multidisciplinary care and the integration between MTB and TB can also help avoid unnecessary adverse effects and unjustified costs to the public healthcare system (Bartoletti et al., 2022) and promote a new concept of cancer genomics, flattening the learning curve of precision medicine.

We propose that multidisciplinary integration should be based on key points, documentation and monitoring of items summarized in Table 3.

In Fig. 1, we provide a CP model that can be scaled up to integrate care settings. After the diagnosis of BC (1), the patient is addressed to TB (2) for case evaluation. After a multidisciplinary discussion of eligibility criteria for genetic testing (3), germline testing (4) is offered if a hereditary syndrome is suspected. If the test is performed and the result is positive, other family members are recommended for testing (5). Finally, the cancer patient and family members at risk (5) are referred to a cancer prevention-specific genetic testing and surveillance program (6).

6.1. Clinical decision making and Molecular Tumor Board

To date, the identification of germline pathogenic variants other than *BRCA1/2* genes influences surveillance strategies in relation to the high risk of developing BC and suggests the indication for oncologic risk reduction through prophylactic surgery only for genes considered high risk (Table 1). However, it does not change the therapeutic strategy of patients affected by BC, except for variants in *TP53*, for which, as mentioned above, the use of radiotherapy is not recommended. PARP inhibitors could be a future approach in those patients with a BC with PALB2 mutation. Moreover, in the future, some such variants could become potential therapeutic targets or be considered predictive of response to certain treatments. In particular, some studies show an association between homologous recombination deficiency (HRD) positive patients and outcomes in patients with triple-negative BC (Chen et al., 2023). For this reason, the indication for performing multigenic panels, and in particular the related treatment strategy, will increasingly need to be evaluated and discussed in a multidisciplinary setting.

The Molecular Tumor Boards (MolTB) are multidisciplinary panels assigning targeted therapies based on genomic tumor profiling, mostly by tumor-agnostic criteria and focused on actionable alteration in patients with advanced tumors and no standard of therapeutic opportunity available for them (Giacomini et al., 2022).

In case of gene mutations of no high-risk category in a multigenic panel or VUS, the function of the MolTB is, to date, to discuss the specific case and assess the presence of these mutations in a more global, non-therapeutic view (to interpret the coincidence of concomitant mutations, to better know the tumor course related to the VUS onset, to study gene non-pathogenic mutations that may be considered of clinical importance in the context of specific biological features of BC). Therefore, since now the discussion of the single case in the MolTB represents an important opportunity to target specific therapies to those patients with known pathogenic mutations.

Table 3
Key points and items for the design of the MTB and TB integrated model.

Key points	Items to be documented and monitored
– Definition of the CP and its integration in a care network – Identification of the case manager – Monitoring CP key steps and impact on care value – Continuous patient monitoring via digital care [www.regione.lazio.it/sites/default/files/documentazione/SAN-DD-G01829–14–02–2023-Allegato1.pdf]	– Somatic driver mutations/copy number/structural variations, including fusion genes – Druggable molecular alterations – Microsatellite instability – Tumor mutation burden – Alterations indicating drug resistance – MTB conclusions/recommendations – Potentially available clinical trials (Luchini et al., 2020) – Variants potentially useful in preventative settings

CP: critical pathway; MTB: Molecular Tumor Board; TB: Tumor Board

7. Concluding remarks

Genetic testing can impact preventive and diagnostic processes for patients with BC (André et al., 2020; Robson et al., 2017) and their blood relatives (Schmidlen et al., 2022; Frey et al., 2022). Its application is increasing worldwide and has an important impact on customized decisions for therapeutic strategies and preventative initiatives, such as organ-specific monitoring and risk-reducing surgery, not only for BC but also for other solid tumors based on specific cancer risk. At the same time, a favorable balance between costs and benefits must be maintained (Peltomaki et al., 2023; Rooney et al., 2023). This has been demonstrated for the high-risk *BRCA1*, *BRCA2* and *PALB2* genes and Lynch syndrome also at the population level (Guzauskas et al., 2023; Guo et al., 2024). Preliminary evidence suggests that MGP may be cost-effective (Silver and Niell-Swiller, 2022), although further studies in this area are needed. Furthermore, it has implications for clinical research, including the accrual of data on VUS, which are needed to clarify their clinical significance. Genetic counseling is a well-established communication process that helps people adjust to the medical, familial, and psychological implications of genetic information and make informed decisions. Although the process of MGP testing can seem overwhelming and cause distress because of uncertainty (Vicuna et al., 2018), positive results that allow for well-defined medical treatment and surveillance protocol are associated with beneficial effects (Ringwald et al., 2016). Currently, the clinical and psychological benefits of including moderate-penetrance genes in MGPs are unclear but may increase once more accurate cancer risk assessments become available and clinical guidelines for preventative management are established (Paluch-Simon et al., 2016). Nevertheless, given the usefulness and accurate but more complex information and consequent implications arising from the detection of PVs and VUS (Lucci-Cordisco et al., 2022) in MGPs, healthcare providers should still consider family history together with genetic information to customize the approach and to avoid inappropriate clinical management.

It is important that genetic testing and counseling be integrated into the clinical management of BC, both in the early and metastatic stages, with clinical geneticists and psycho-oncologists included in the multidisciplinary disease management (Biganzoli et al., 2020). As already established for *BRCA1/2* in Italy (Cortesi et al., 2020], a Hub and Spoke model for different VP carriers should be envisioned at the regional level with screening programs involving general practitioners and specialists. As a complex disease, BC requires a care model with a multidisciplinary perspective, and a CP model has been proposed for patients with BC with a PV in specific genes other than *BRCA1/2* (Giacomini et al., 2022). In a value-based BC healthcare system, a shared decision-making framework would ensure that patients play an active role, considering their preferences and goals. Therefore, it should be implemented as a routine in clinical practice, logistics and operations, and digital support systems.

In conclusion, the management of PVs and VUS in non-*BRCA1/2* CPGs included in MGPs represents a crucial but unmet need for BC treatment, which requires a well-defined multidisciplinary and integrated approach, considering the continuous evolution of guidelines and research updates in the field.

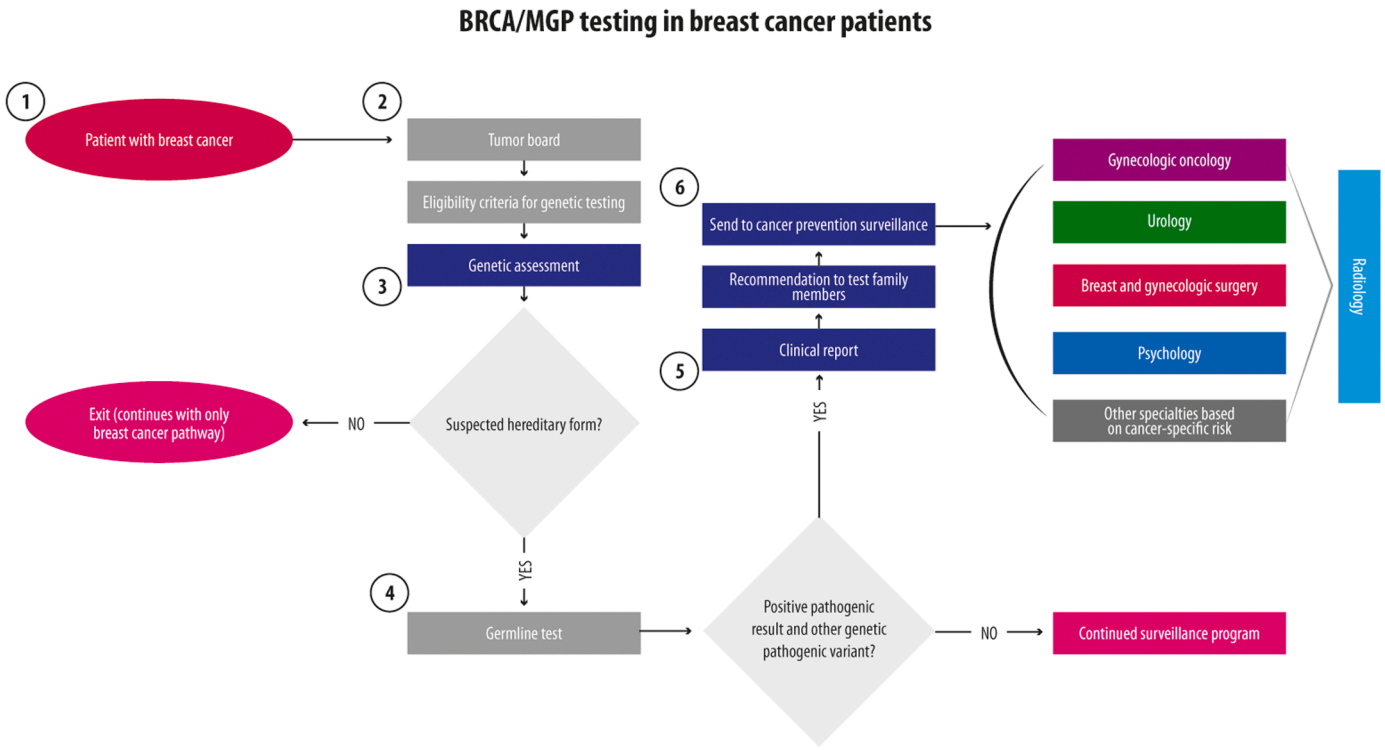

Fig. 1. The most relevant steps of an integrated, multidisciplinary approach to clinical management of genetic variants in breast cancer.

Critical View

In the complex scenario of high and moderate/intermediate penetrance genes predisposing to breast cancer, clinical management via a multidisciplinary approach has increasingly been needed and applied worldwide. In this narrative review, we aimed to discuss critically the clinical utility of multigenic panels and the clinical management of patients with PVs other than *BRCA1/2* and with VUS, as well as the available evidence regarding the multidisciplinary and integrated management, proposing key points and items to be documented and monitor for an effective realization. Considering the continuous evolution of guidelines and research updates in the field, here we provided an updated overview of the current state of breast cancer treatment and highlighted the crucial but unmet need of managing PVs and VUS in non-*BRCA1/2* CPGs via a defined multidisciplinary integrated approach.

Ethics approval

Not required

CRediT authorship contribution statement

Conceptualization: AF, MG, SD. Data Curation: AF, MG, LC, SD. Supervision: AF, MG, SD. Manuscript writing: AF, LC, SD, ELC, IP, AGDB, AO, FM, MM, PF, MG. Manuscript Editing: All, Approval to submit: All.

Declaration of Competing Interest

no conflict

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