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Clinical Impact of Constitutional Genomic Testing on Current Breast Cancer Care

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Abstract

The most commonly diagnosed cancer in women worldwide is cancer of the breast. Up to 20% of familial cases are attributable to pathogenic mutations in high-penetrance (BReast CAncer gene 1 [BRCA1], BRCA2, tumor protein p53 [TP53], partner and localizer of breast cancer 2 [PALB2]) or moderate-penetrance (checkpoint kinase 2 [CHEK2], Ataxia-telangiectasia mutated [ATM], RAD51C, RAD51D) breast-cancer-predisposing genes. Most of the breast-cancer-predisposing genes are involved in DNA damage repair via homologous recombination pathways. Understanding these pathways can facilitate the development of risk-reducing and therapeutic strategies. The number of breast cancer patients undergoing testing for pathogenic mutations in these genes is rapidly increasing due to various factors. Advances in multigene panel testing have led to increased detection of pathogenic mutation carriers at high risk for developing breast cancer and contralateral breast cancer. However, the lack of long-term clinical outcome data and incomplete understanding of variants, particularly for moderate-risk genes limits clinical application. In this review, we have summarized the key functions, risks, and prognosis of breast-cancer-predisposing genes listed in the National Health Service (NHS) England National Genomic Test Directory for inherited breast cancer and provide an update on current management implications including surgery, radiotherapy, systemic treatments, and post-treatment surveillance.

Key words: Genomic testing; breast cancer predisposing genes; germline variants

Introduction

Breast cancer is the most diagnosed cancer in women worldwide. It is now estimated that about 20% of breast cancers are familial, with high-penetrance inherited cancer-predisposing genes such as BReast CAncer gene1/2 (*BRCA1/2*), tumor protein p53 (*TP53*), and partner and localizer of breast cancer 2 (*PALB2*), accounting for approximately 30% of heritable breast cancer cases [1], or around 6% overall [2]. The remaining familial cases are attributable to moderate-penetrance (e.g., checkpoint kinase 2 [*CHEK2*], Ataxia-telangiectasia mutated (*ATM*), *RAD51C/D*) and low-penetrance genes or single-nucleotide polymorphisms (SNPs) [3,4].

Recognition that specific breast cancer phenotypes are associated with underlying high-risk gene mutations [5] has increased referrals for testing. The evolution and refinement of carrier probability models and the increased capacity and reduced costs of genomic testing have lowered the UK risk threshold for *BRCA* mutation testing from 20% to 10% [6]. Establishment of *BRCA* status as a biomarker of response to platinum chemotherapy and poly-ADP ribose polymerase (PARP) inhibitors is driving testing of more patients who could benefit from these treatments [7,8].

Recent advances in sequencing technologies and multi-gene panel testing have resulted in more comprehensive testing of increasing numbers of genes than performed historically [9]. Therefore, it is important to consider retesting with modern methods in patients who have previously tested negative but have been diagnosed with a new breast cancer with clinical features suggestive of an underlying high-penetrance cancer-predisposing gene.

In this review, we focus primarily on the genes currently listed in the UK National Health Service (NHS) National Genomic Test Directory R208 for inherited breast cancer (*BRCA1*; *BRCA2*; *PALB2*; *CHEK2*; *ATM*; *RAD51C*; *RAD51D)* and provide an update on current management implications of pathogenic mutations in these genes including surgery,

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radiotherapy (RT), systemic treatments (Table 1), and post-treatment surveillance [10]. The surgical management of inherited cancer-predisposing genes in patients without personal history of cancer is discussed elsewhere [11]. Other rare high-penetrance genes associated with hereditary cancer predisposition syndromes (e.g., *PTEN*, *STK11*, *CDH1*) have been excluded from this review, with the exception of *TP53*.

BReast CAncer Gene 1/2

BRCA1 and *BRCA2* were the first genes to be associated with hereditary breast cancer [12,13]. They are autosomal dominantly inherited tumor-suppressor genes involved in double-stranded DNA (dsDNA) break repair by homologous recombination (HR) (Figure 1). Population frequency of pathogenic mutation carriers is estimated at 0.2–0.3% rising to 2% in the Ashkenazi Jewish population [14].

Compared to sporadic cancers, *BRCA1*-associated tumors tend to be higher-grade, hormone-receptor, and HER2-negative [15,16]. While 15–20% of all breast cancers are triple-negative, up to 60–70% of *BRCA1*-associated tumors exhibit this phenotype [17]. *BRCA2*-associated tumors are less distinct, typically high-grade ductal; however, several studies have noted the higher proportion of tumors that have a lobular-type histology and are human epidermal growth factor receptor 2 (HER2)-negative compared with noncarriers [16,18–20]. *BRCA*-associated breast cancers are more frequently multifocal/multicentric than sporadic cancers, more so in *BRCA2*-associated than in *BRCA1*-associated cancers [21].

BRCA mutation carriers have an estimated lifetime breast cancer risk of 60–80% [22–25]. Multiple published retrospective studies have yielded inconsistent oncological outcomes in *BRCA1/2* mutation carriers, showing same, better, and worse outcomes than sporadic cancer patients. A meta-analysis involving 35,972 breast cancer patients, including 3402 *BRCA1/2* mutation carriers, showed worst survival outcomes in *BRCA* mutations carriers (*BRCA1* overall survival [OS]; hazard ratio [HR]: 1.2; 95% confidence interval [CI]: 1.08–1.33; $p < 0.001$) (*BRCA2* disease-free survival [DFS]; HR: 1.35; 95% CI: 1.1–1.67; $p = 0.0049$) [26]. Studies included have significant limitations including survivor bias and failure to adjust for age, treatment, or pathological factors. The UK POSH study, one of the largest prospective population-based cohort studies, showed no significant difference in OS or distant DFS between *BRCA1/2* carriers and noncarriers for young breast cancer patients (age: 40 and younger) diagnosed with early breast cancer at a median follow-up of 8.2 years [27,28]. There appeared to be an early survival advantage for *BRCA* carriers diagnosed with triple-negative breast cancer (TNBC).

Most published studies conclude that *germline BRCA mutation (gBRCA)* carriers have higher rates of in-breast tumor events (local recurrences or new primary cancers) and contralateral breast cancer (CBC) but no increased radiation toxicity [29–33]. Thus, *gBRCA* patients opting for breast-conserving surgery (BCS) can be offered RT, provided they are well informed about the significantly elevated risks of in-breast tumor events and CBC compared to noncarriers with a similar cancer. RT is usually, but not always, recommended after BCS, whereas RT to the chest wall is recommended for some, but not all, patients after mastectomy. It is therefore possible that some patients who, based on their personal and tumor characteristics, would be recommended RT as part of BCS but not postmastectomy, might opt for immediate risk-reducing surgery at the time of their cancer oncological surgery to avoid RT and the consequent impact of this on any breast reconstruction and reconstructive options planned. Patients choosing BCS should be offered more intensive surveillance imaging corresponding to their individual risk [6].

With increased access to *BRCA1/2* testing, the shared decision-making process should ensure that patients fully understand the benefits and risks associated with different management approaches. The timing of risk-reducing options should consider the context (e.g., primary breast cancer prognosis, age, and comorbidities) for each individual. The discussion can be influenced by *BRCA*-testing turnaround time [34]. Cancer patients without family history offered immediate genetic testing and opting for risk-reducing surgery may experience more decisional regret and require additional psychological support [35]. The POSH study showed that immediate risk-reducing mastectomy (RRM) for symptomatic breast cancer was not associated with short-term/medium-term survival benefit; therefore, patients may choose to delay surgery until they are better prepared for the biopsychosocial consequences [28]. There is currently no evidence on the appropriate end date for surveillance post BCS. This, coupled with the lack of evidence to support continued surveillance following RRM may influence patient decision-making [36].

Recognition of the role of *BRCA* in dsDNA repair led to the hypothesis that *BRCA*-associated tumors are particularly sensitive to platinum-based chemotherapies that directly bind DNA. The randomized-controlled TNT (triple negative tumour) trial demonstrated that *BRCA* mutation carriers with metastatic triple-negative breast cancer (mTNBC) responded significantly better to carboplatin than to noncarriers [37]. However, in the neoadjuvant setting, all patients with TNBC benefit from platinum-based chemotherapy, regardless of *BRCA* status [38]. Currently, there is no consensus on the use of platinum chemotherapy in the neo-/adjuvant treatment of non-triple-negative breast tumors in *BRCA1/2* carriers [39].

Poly ADP ribose polymerase inhibitors (PARPis) such as olaparib/talazoparib are targeted cancer therapies designed to exploit the dsDNA-repair deficiency associated with *gBRCA* mutations. The OlympiAD and EMBRACA trials have demonstrated the benefit of olaparib and talazoparib, respectively, in treating metastatic breast cancer patients with *gBRCA* mutations, with improved progression-free survival compared to treatment of physician's choice [40,41]. Additionally, the OlympiA trial demonstrated the efficacy of adjuvant olaparib in early high-risk breast cancer with an improved DFS [42]. This led to UK NICE approval and subsequent amendment of the UK National Genomic Test Directory to allow testing in patients who do not meet

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Table 1
Characteristics and management strategy for germline mutations associated with hereditary breast cancer

Gene	Function	Tumor phenotype	Population frequency	Estimated lifetime risk of breast cancer	Screening recommendations	Surgical implications	RT implications	Systemic therapy implications
BRCA1	Combines with other tumor suppressors to form the *BRCA* complex, repair of dsDNA breaks by HR	Strongly associated with TNBCs	0.2–0.3% (up to 2% in Ashkenazi Jewish populations)	60–80%	Annual screening from age 30	High risk of in-breast tumor events. Discuss RRM.	No contraindications to use.	Evidence of PARPi efficacy in HER2-negative disease in early/metastatic setting. Platinum-based chemotherapeutic agents effective in triple-negative disease.
BRCA2	Interact with *BRCA1*, *PALB2*, and *RAD51* to form *BRCA* complex	Association with HER2-negative and lobular cancers	0.2–0.3% (up to 2% in Ashkenazi Jewish populations)	60–80%	Annual screening from age 30	High-risk of in-breast tumor events. Discuss RRM.	No contraindications to use.	Evidence of PARPi efficacy in HER2-negative disease in early/metastatic setting. Platinum-based chemotherapeutic agents effective in triple-negative disease.
PALB2	Major *BRCA2*-binding partner, connecting *BRCA* complex and facilitate *RAD51* function	ER-positive, HER2-negative; triple-negative cancers	0.12%	33–58%	Annual screening from age 30	High-risk of in-breast tumor events. Discuss RRM.	No contraindications to use.	Ongoing PARPi trials. Case series showing good response to carboplatin in metastatic setting.
CHEK2	Cell cycle checkpoint regulation, interacts downstream with *BRCA1*, p53 and Cdc25c	ER-/PR-receptor positive; HER2-positive	0.5–1% (In Northern European populations)	20–37%	Annual screening from age 40	Insufficient evidence for RRM, manage based on individual risk/family history.	No contraindications to use. Limited data showing increased contralateral BC from prior RT use. Decision for use to be based on conventional clinical and pathological factors.	No difference between anthracycline and non-anthracycline-based chemotherapy. Ongoing PARPi trial.

(*continued on next page*)

Table 1 (*continued*)

Gene	Function	Tumor phenotype	Population frequency	Estimated lifetime risk of breast cancer	Screening recommendations	Surgical implications	RT implications	Systemic therapy implications
ATM	Initiates signaling cascade for HR repair	ER-positive, HER2-negative	0.4–1%	25–35%	Annual screening from age 40	Insufficient evidence for RRM, manage based on individual risk/ family history.	Avoid in homozygous carriers due to profound sensitivity. Contralateral breast cancer risk possibly increased due to prior RT use in rare missense variants. No strong evidence to suggest contraindication in more common pathogenic variants.	Ongoing PARPi trial. Limited number showing worst survival and progression-free survival with CDK4/6 use.
RAD51	Forms complex with paralogs and interact with *BRCA1/2* at site of DNA damage	TNBCs	0.04–0.05%	15–20% (up to 40% with positive family history)	Annual screening from age 40 (can differ depending on individual risk)	Insufficient evidence for RRM, manage based on individual risk/ family history	No reported contraindications.	Ongoing PARPi trial.
TP53	Encodes tumor suppressor which acts as an important cell cycle checkpoint regulator, suppressing proliferation or inducing apoptosis	HER2-positive and mixed ductal and lobular cancers	0.005%	40–80%	Annual screening from age 20	Mastectomy preferred over BCS due to high risk associated with RT. High-risk of in-breast tumor events. Discuss RRM	High risk of radiation-induced secondary malignancies. Avoid use where possible.	Limited data showing potential efficacy of carboplatin-based chemotherapy over anthracycline or taxane-based chemotherapy in neoadjuvant setting.

Abbreviations: *TP53* = tumor protein p53; RRM = risk-reducing mastectomy; HR = homologous recombinant; BCS = breast-conserving surgery; TNBC = triple-negative breast cancer; CHEK2 = checkpoint kinase 2; *BRCA1/2* = BReast CAncer gene 1/2; *ATM* = Ataxia-telangiectasia mutated; ER = estrogen receptor; PR = progesterone receptor; *PALB* = partner and localizer of breast cancer; dsDNA = double-stranded DNA; PARPi = poly ADP ribose polymerase inhibitor; HER = human epidermal growth factor receptor.

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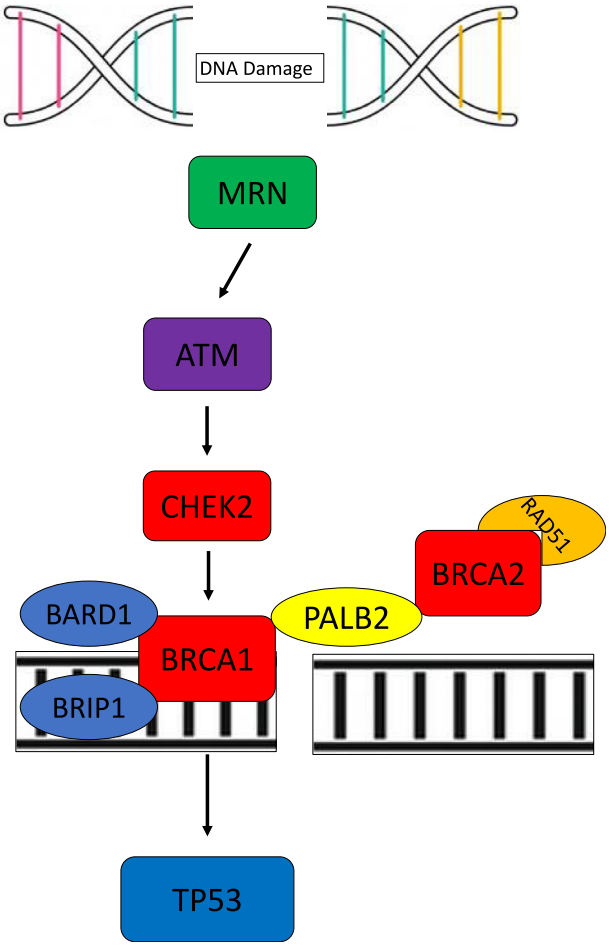

Fig 1. The relationship of homologous recombinant (HR) genes in response to DNA damage. Double-stranded DNA breaks are recognized by the Mre11-RAD50-Nbs1 (MRN) complex, which recruits and activates ATM. ATM initiates the HR signaling cascade involving downstream proteins including CHEK2, BRCA1, and p53. CHEK2 phosphorylates >20 proteins that interact with BRCA1. Phosphorylated BRCA1 activates HR, in cooperation with BRCA2 and RAD51, and interacts with numerous proteins including BARD1 and BRIP1 to modulate DNA repair. PALB2 serves as a major binding partner of BRCA2, forming the BRCA complex and facilitating RAD51-mediated strand exchange.
Abbreviations: *BRCA1/2 = BReast CAncer gene 1/2; PALB = partner and localizer of breast cancer; ATM = Ataxia-telangiectasia mutated; CHEK2 = checkpoint kinase 2.*

the R208 criteria, but would be eligible for olaparib if they tested positive for a *gBRCA1/2* mutation, under the R444 criteria [10,43].

Partner and Localizer of Breast Cancer 2

PALB2 is a tumor-suppressor gene involved in the HR repair pathway serving as a *BRCA2*-binding partner, connecting the *BRCA* complex (*BRCA1-PALB2-BRCA2-RAD51*) and facilitating *RAD51* function (Figure 1) [44]. Biallelic mutations in *PALB2* result in recessively inherited Fanconi anemia, whereas monoallelic mutations predispose carriers to various cancers including breast, ovarian, and pancreatic cancers [45,46]. Over 600 distinct *PALB2* variants have been identified; however, only approximately 140 of them are pathogenic, leaving >400 missense variants of unknown significance (VUSs), which presents challenges in variant interpretation and genetic counseling [47,48].

Pathogenic *PALB2* variants are identifiable in approximately 0.66–2% of breast cancer cases worldwide, higher in familial cases [49]. *PALB2* carriers are considered to have a high–moderate breast cancer risk (≥4-fold higher risk than base population) [50]. An international study involving 524 families, including familial and unselected breast cancer cases, determined an absolute breast cancer risk of 52.8% (95% CI: 43.7%–62.7%) by the age of 80 [51].

PALB2 mutations are associated with larger, high-grade, advanced-stage estrogen receptor (ER)-positive, HER2-negative cancers than are sporadic cases (odds ratio [OR]: 9.43; 95% CI: (6.24–14.25) resembling the pattern in *BRCA2* carriers, possibly reflecting the closely associated functions of these genes.

Population screening in China revealed a shorter OS for *PALB2*-mutation carriers than that for noncarriers (adjusted HR: 8.38; 95% CI: 2.19–32.11; p = 0.002) [52]. Intriguingly, a prospective study focusing on CBC risks showed that the 10-year cumulative incidence of CBC in *PALB2* carriers was 7.9% (3.8–16.1) compared to *BRCA1* at 23.1% (16.4–32.6) and *BRCA2* at 16.9% (11.8–24.3), but among *PALB2* carriers whose initial breast cancer was ER-negative, the CBC risk was estimated at 19.7% (9.4–41.1) [53].

There is a lack of clinical studies reporting surgical outcomes in *PALB2*-mutation carriers. Due to the high lifetime and CBC risk, bilateral (prophylactic) mastectomy or contralateral RRM may be considered, especially in high-risk families. However, the patient–clinician discussion should be clear that while risk-reducing surgery may reduce the risk of future primary breast cancers, there is currently no evidence that it improves OS compared to enhanced surveillance (annual magnetic resonance imaging [MRI] and/or mammography). The decision to discontinue surveillance (post-BCS) should be based on individual factors including breast density, comorbidities, and patient adherence to the surveillance protocol [36].

Despite the role of *PALB2* in DNA repair, there are no reports of adverse outcomes or toxicity with the use of RT, and the decision-making process for RT should be based on standard clinicopathological characteristics. However, given the known association of radiation hypersensitivity in Fanconi anemia patients, any occurrence of acute radiation toxicities in a *PALB2* pathogenic mutation carrier should prompt a medical review of the patient to assess whether there are any clinical features of Fanconi anemia and further interrogation of germline DNA sequence to look for a pathogenic *PALB2* variant in the opposite allele.

The close relationship between *PALB2* and the *BRCA* genes has triggered studies of the efficacy of platinum chemotherapy and PARPi in *PALB2* carriers [54]. A series of two patients with germline *PALB2* mutations showed excellent response to adjuvant platinum-based agents in the metastatic setting [55]. Several Phase II trials are underway to evaluate PARPi (olaparib/talazoparib) in mTNBC

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patients with non-*BRCA* germline HR genes, including *PALB2*. PARPi are not currently licensed for use in non-g*BRCA* patients for breast cancer.

Checkpoint Kinase 2

The checkpoint kinase 2 (*CHEK2*) gene is a tumor-suppressor gene that encodes a protein kinase that phosphorylates >20 proteins and interacts downstream with the *BRCA1*, *p53*, and *Cdc25c* pathways involved in cell cycle checkpoint regulation, inhibition of cellular proliferation, and activation of DNA repair pathways [56].

Several *CHEK2* pathogenic protein-truncating variants have been linked to a moderate increased breast cancer risk (two- to three-fold above population baseline risk). There are many VUSs commonly reported in multigene panels; however, that does not significantly increase breast cancer susceptibility [57,58]. Pathogenic variants, such as the c.1100delC loss-of-function variant, are most prevalent in individuals of European ancestry, with a population frequency of 0.5–1% in Northern Europe [59]. The cumulative lifetime risk of breast cancer in *CHEK2* carriers varies between 20 and 37% by the age of 70, depending on family history [60,61].

CHEK2 variants are mostly associated with hormone-receptor-positive and HER2-positive breast cancer and more aggressive breast cancers compared to sporadic cancers, with a tendency toward younger onset, multifocality, higher degree of nodal involvement, and bilateral disease at presentation [17,58,62]. Intriguingly, the relative risk of *CHEK2*-associated breast cancers decreases significantly with age [58,59,63].

Data from the Breast Cancer Association Consortium (BCAC) revealed a significantly elevated risk of breast-cancer-specific death (HR: 1.63; 95% CI: 1.24–2.15; $p < 0.001$) in *CHEK2* carriers compared to that in noncarriers [64]. Similarly, *CHEK2* carriers also had worse OS (at 10 years, 60.7%, 95% CI: 42.5–74.8) than noncarriers (OS: 70.2%; 95% CI: 67.8–72.5) in a young-onset early breast cancer cohort [62]. Several studies have demonstrated an approximately two-fold risk of CBC in *CHEK2* carriers (a 10-year cumulative incidence of 7.9%) [53,64,65]. Since most *CHEK2*-associated breast cancers are ER-positive, adjuvant endocrine therapy is associated with a reduced incidence in CBC, with an effect size similar to that of sporadic ER+ breast cancers [66].

Limited case series have shown similar locoregional recurrence rates after BCS+RT for *CHEK2* carriers compared to that for noncarriers [67]. It is still recommended, however, that *CHEK2* carriers undergo an enhanced surveillance programme with annual mammography/MRI post BCS [36]. Currently, RRM is recommended only for high-risk individuals whose risk of developing breast cancer exceeds 30%; considering factors such as age at diagnosis, family history, menopausal status, hormonal receptors of initial cancer, cosmesis and patient preference, and motivation to adhere to an enhanced surveillance programme [6].

There are no reports of distinct radiosensitivity in *CHEK2* mutations or long-term complications except for one study of 233 bilateral breast cancer patients including 15 *CHEK2**1100delC-mutation carriers, reporting an increased risk of CBC in the irradiated *CHEK2* carriers (OR: 6.5; 95% CI: 1.5–28.8; $p = 0.005$) [68]. This has not yet been substantiated, and the use of RT in *CHEK2* carriers should be based on conventional clinicopathological factors.

Some studies have investigated the chemosensitivity of *CHEK2*-associated cancer. Studies including patients with the *CHEK2* c.1100delC mutation showed no difference in response to anthracycline/non-anthracycline-based regimens compared with non-carriers [69,70]. Currently, there are no published studies of platinum-based agents in *CHEK2*-associated breast cancer. A Phase II study evaluating olaparib in HR-related genes including *CHEK2* failed to observe a response in the metastatic setting, although this was limited by sample size [71]. Overall, the sensitivity of *CHEK2*-associated breast cancer to specific treatment regimens remains unclear and warrants further development of clinical trials stratified by *CHEK2* status.

Ataxia-telangiectasia Mutated

The Ataxia-telangiectasia mutated (*ATM*) gene encodes a serine threonine kinase that initiates the signaling cascade for HR repair involving downstream effector proteins including *BRCA1/2*, *PALB2*, *CHEK2*, and p53 in response to dsDNA breaks (Figure 1) [72,73]. Biallelic mutations cause the autosomal recessive Ataxia-telangiectasia (AT) neurodegenerative disorder, characterized by cerebellar ataxia, oculomotor abnormalities, increased malignancies, and profound radiosensitivity.

Monoallelic pathogenic heterozygous *ATM* mutations are present in approximately 0.4–1% of the general population. They are associated with a moderately increased breast cancer risk of two- to three-fold above the population level, with an estimated lifetime risk of 25–35% [74,75]. Data from the CARRIERS consortium of >15,104 patients, including 116 ATM carriers, concluded that *ATM* pathogenic variants were not significantly associated with CBC (a 10-year cumulative incidence of 4.0%) [53]. One missense pathogenic variant c.7271T > G appears to confer a higher risk than do other variants (OR: 3.76; 95% CI: 2.76–5.12), with estimates of cumulative lifetime risk similar to *BRCA2* [76].

The large-scale sequencing study, BRIDGES, revealed a strong association between *ATM* mutations and ER-positive, HER2-negative high-grade tumors (OR: 4.99; 95% CI: 3.68–6.76) compared to sporadic cases, although ER-positive, HER2-negative low-grade tumors were the most common [17].

There is a lack of survival and surgical outcome data on *ATM*-associated breast cancers. Currently, there is insufficient evidence to recommend RRM, and the decision should be guided by family history. An exception is the c.7271T > G variant, where RRM should be discussed, in line with other high-penetrance genes. *ATM* carriers are recommended to adhere to an enhanced surveillance program post BCS with annual mammogram/MRI [36].

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Concerns regarding potential excess toxicity of RT in *ATM* heterozygous carriers have been investigated. The WECARE population-based case–control study reported on a small number of patients in the cohort with ATM pathogenic/likely pathogenic variants showing an increase in CBC risk for carriers that was slightly higher in those receiving RT (cumulative 10-year incidence: 7.4% [2.0–27.8) versus 10.5% [3.9–28.2]) [77]. Another study, including 91 ATM carriers (23 pathogenic and 68 VUSs), found no evidence of increased toxicity or secondary/contralateral cancers (a median follow-up of 32 months) [78]. Among the seven patients diagnosed with CBC at a median 8 years after RT, six were VUS carriers. Overall, current evidence suggests that RT is safe for pathogenic *ATM* mutation carriers [79].

There are currently no published reports on platinum-based agents in *ATM*-associated breast cancer. The effectiveness of PARPi in *ATM*-associated metastatic breast cancer is under investigation [71]. Limited retrospective data from a study evaluating cyclin-dependent kinase (CDK) 4/6 inhibitors in four patients with *ATM* mutations showed that HR gene carriers with advanced ER-positive, HER2-negative breast cancer had the worst survival and progression-free survival outcomes compared to noncarriers [80].

RAD51C/RAD51D

The *RAD51* gene is another important DNA-repair gene in the HR pathway. *RAD51C/D* encodes a key protein that forms a complex with accessory paralog proteins that interact with *BRCA1* and *BRCA2* to facilitate DNA repair at the damage site. *BRCA2* contains *RAD51*-binding domains and promotes *RAD51*-dependent strand exchange [81].

A population analysis study involving 60,466 breast cancer patients and 53,461 controls detected pathogenic variants of *RAD51C* and *RAD51D* in 0.11% and 0.10% of breast cancer patients and 0.05% and 0.04% in controls (OR: 1.93; $p = 0.0070$ and 1.80; $p = 0.018$), respectively [82]. Pathogenic variants, such as *RAD51D* c.270_271dupTA, are estimated to confer a moderately increased lifetime breast cancer risk of 15–40%, which can vary significantly depending on family history [83]. Current UK guidelines recommend using risk-prediction tools such as CanRisk to determine age-specific risks for directing screening and management strategies [84].

The tumor subtype distribution of *RAD51C* and *RAD51D* is similar. *RAD51C/D* mutations are strongly associated with TNBC (OR range: 5.71–6.19) as opposed to ER-positive, HER2-negative tumors (OR range: 1.17–1.52) [17,82]. *RAD51D* carriers tend to have a more aggressive profile, including positive axillary lymph nodes, high-grade tumors, and earlier onset of breast cancer (mean age: 45.4 years), similar to *BRCA1/2*-carriers, than noncarriers (51.3 years) [85]. *RAD51D* carriers also had worse survival outcomes in terms of recurrence-free survival (unadjusted HR: 3.00; 95% CI: 1.56–5.80; $p = 0.001$) than noncarriers.

Despite the lack of data on surgical outcomes and CBC risk in *RAD51C/D* carriers, the substantial lifetime risk of breast cancer associated with a positive family history supports discussion of RRM. Following a UK-wide consensus meeting, the UK Cancer Genetics Group (UKCGG) issued guidelines recommending clinicians discuss RRM if the lifetime risk exceeds 30% following an individualized risk assessment and appropriate counseling in *RAD51C/D* pathogenic variant carriers without personal history of breast cancer [84,86]. The role of contralateral RRM in improving OS for high-penetrance genes remains controversial despite being effective in reducing CBC risk, perhaps even more so with respect to moderate-penetrance genes such as *RAD51C/D*.

There are limited data on the use of RT in *RAD51C/D* mutations. However, the *RAD51* genes form part of the *BRCA* complex (*BRCA1-PALB2-BRCA2-RAD51*) and despite their role in DNA repair, there are no reported toxicities in the other genes of the complex [87]. Therefore, the use of RT in breast cancer patients with *RAD51C/D* mutations should be individualized and based on classic clinical and pathological factors.

There are currently no published clinical reports on use of platinum-based agents in *RAD51C/D*-associated breast cancer. *RAD51C/D* mutations are hypothesized to exhibit similar sensitivity to PARPi [88]. A Phase II trial (ClinicalTrials.gov NCT02401347) is underway evaluating the use of the PARPi talazoparib in non-*BRCA1/2* HR pathway genes including *RAD51C/D*.

Tumor Protein p53

Tumor protein p53 (*TP53*) is a crucial tumor-suppressor gene that regulates cell cycle checkpoints by regulating the transcription of numerous genes that subsequently suppress proliferation or induce apoptosis following DNA damage [89]. Pathogenic *gTP53* variants are associated with Li–Fraumeni syndrome (LFS), a rare autosomal, dominantly inherited cancer predisposition syndrome associated with various early-onset primary cancers, including central nervous system tumors, bone and soft tissue sarcomas, adrenocortical carcinomas, gastrointestinal, and lung, prostate and breast cancers [90,91].

Breast cancer is the most frequent cancer in adult female *TP53*-carriers. While the frequency of pathogenic *TP53* variants in the general population is estimated at 1 in 20,000 (0.005%), data from the CARRIERS consortium and BCAC identified pathogenic *TP53* variants in 19 of 32,247 (0.06%) and 7 of 48,826 (0.01%) unselected breast cancer patients [82,83,92]. *TP53* pathogenic variants confer a 20- to 40-fold increased breast cancer risk between ages 20 and 40, with an estimated cumulative incidence of approximately 85% by the age of 60 [92,93].

A unique study comparing LFS patients with a pathogenic *TP53* mutation to a cohort of early young onset breast cancer showed that TP53 carriers were more likely to have hormone-receptor and HER2-positive (triple-positive) breast tumors (42% vs 8%; $p = 9.3 \times 10^{-5}$) [94]. Furthermore, data from BRIDGES also demonstrated that *TP53* carriers were more likely to develop HER2-positive tumors (45% of cases), and mixed lobular and ductal tumors rather than pure ductal carcinoma subtypes [17]. Given the association of *TP53* with HER2-positive and YOBC, patients aged <30

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(or <35 for HER2-positive breast cancer) who test negative for other breast-cancer-predisposing genes are eligible for LFS testing under the UK National Genomic Testing Directory R216 [10].

There are limited studies on clinical outcomes of *gTP53* mutation carriers. A Chinese study of 10,053 early-stage breast cancer patients, including 50 *gTP53* patients, revealed worse survival outcomes in terms of relapse-free survival (HR: 2.24; 95% CI; 1.15–4.33; $p = 0.02$) and OS (HR: 4.6; 95% CI: 2.26–9.41; $p < 0.001$) than sporadic and wild-type *TP53* cases [95]. Studies assessing the risk of developing CBC have shown significantly elevated 10-year cumulative risks, ranging from 17.9–53%, depending on population selection [96,97].

Several studies have shown a significantly elevated risk of radiation-induced secondary malignancies, up to 30%, in *TP53* carriers receiving adjuvant RT [98–100]. Secondary malignancies documented include sarcomas and thyroid cancers. Therefore, current guidelines recommend avoiding RT whenever possible, favoring mastectomy over BCS [101]. Use of RT should be considered on an individualized basis, following a multidisciplinary team discussion, for cases with a significant risk of locoregional recurrence post mastectomy in pathogenic *gTP53* carriers.

The European Reference Network GENTURIS has issued guidelines recommending the use of nongenotoxic chemotherapies due to the potential risk of developing new malignancies with genotoxic chemotherapies, as demonstrated in an LFS mouse model [102,103]. A Chinese study including 50 *TP53*-carriers in an unselected breast cancer population showed a higher rate of pathological complete response in *TP53*-carriers treated with taxane–carboplatin–based neoadjuvant chemotherapy compared to anthracycline- or taxane-based chemotherapy (50% vs 0%; $p = 0.006$) [95]. There are currently no published reports on the treatment response to targeted therapy despite the association of *TP53* with HER2-positive breast cancers.

Conclusion

Knowledge of the relevance of inherited pathogenic variants for treatment and surveillance decisions is increasing and for selected patients, and early germline genetic testing at the time of breast cancer diagnosis may contribute to optimal treatment planning. However, the very small number of less frequently identified germline pathogenic variants often result in a lack of certainty regarding effect sizes and wide confidence intervals around risk estimates. More large-scale prospective long-term outcome data are needed, particularly on a national basis, with linkage to genetic data to enable very large cohort studies for assessing risks and clinical outcomes.

Author contribution

Dr. Wilson Pui Fui CHEAH: writing—original draft.
Prof. Ramsey I CUTRESS: writing—review and editing.
Prof. Diana ECCLES: writing—review and editing.
Prof. Ellen COPSON: writing—review and editing.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Prof. Ellen Copson reports a relationship with AstraZeneca that includes consulting or advisory and funding grants. Prof. Ellen Copson reports a relationship with Eli Lilly that includes consulting or advisory. Prof. Ellen Copson reports a relationship with Pfizer that includes consulting or advisory. Prof. Ellen Copson reports a relationship with Menarini Stemline UK that includes consulting or advisory. Prof. Ellen Copson reports a relationship with Roche that includes consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Prof. Ellen Copson reports a relationship with Novartis that includes consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Prof. Ellen Copson reports a relationship with Daiichi Sankyo that includes funding grants. Prof. Ellen Copson reports a relationship with SECA that includes funding grants and nonfinancial support. Prof. Ellen Copson reports a relationship with World Cancer Research Fund that includes consulting or advisory. Prof. Ramsey Cutress reports a relationship with SECA that includes: funding grants. Prof. Ramsey Cutress reports a relationship with AstraZeneca that includes: funding grants. Prof. Diana Eccles reports a relationship with AstraZeneca that includes funding grants. Coauthor is a trustee of Association of Breast Surgery (ABS), R.I.C. Coauthor is a nonexecutive director of the University Hospitals Southampton NHS Foundation Trust Board, D.E.

References

[1] Reid S, Spalluto LB, Lang K, Weidner A, Pal T. An overview of genetic services delivery for hereditary breast cancer. *Breast Cancer Res Treat* 2022;191:491–500. https://doi.org/10.1007/s10549-021-06478-z.

[2] Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. *Clin Epidemiol* 2019;11:543–561. https://doi.org/10.2147/CLEP.S206949.

[3] Sarhangi N, Hajjari S, Heydari SF, Ganjizadeh M, Rouhollah F, Hasanzad M. Breast cancer in the era of precision medicine. *Mol Biol Rep* 2022;49:10023–10037. https://doi.org/10.1007/s11033-022-07571-2.

[4] Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, *et al*. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol* 2017;3:1190. https://doi.org/10.1001/jamaoncol.2017.0424.

[5] Gorski JJ, James CR, Quinn JE, Stewart GE, Staunton KC, Buckley NE, *et al*. BRCA1 transcriptionally regulates genes associated with the basal-like phenotype in breast cancer. *Breast Cancer Res Treat* 2010;122:721–731. https://doi.org/10.1007/s10549-009-0565-0.

[6] National Institute of Clinical Excellence. Clinical Guideline 164. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family

history of breast cancer (updated 2019). n.d., https://www.nice.org.uk/Guidance/CG164. [Accessed 7 August 2023].

[7] Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, *et al*. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018;24:628–637. https://doi.org/10.1038/s41591-018-0009-7.

[8] Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, *et al*. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. *New Engl J Med* 2017;377:523–533. https://doi.org/10.1056/NEJMoa1706450.

[9] Desmedt C, Voet T, Sotiriou C, Campbell PJ. Next-generation sequencing in breast cancer: first take home messages. *Curr Opin Oncol* 2012;24:597–604. https://doi.org/10.1097/CCO.0b013e328359554e.

[10] National Genomic Test Directory. Rare and inherited disease eligibility criteria, https://www.england.nhs.uk/publication/national-genomic-test-directories/2023. [Accessed 7 August 2023].

[11] McCarthy RL, Copson E, Tapper W, Bolton H, Mirnezami AH, O'Neill JR, *et al*. Risk-reducing surgery for individuals with cancer-predisposing germline pathogenic variants and no personal cancer history: a review of current UK guidelines. *Br J Cancer* 2023. https://doi.org/10.1038/s41416-023-02296-w.

[12] Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, *et al*. A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*. *Science (1979)* 1994;266:66–71. https://doi.org/10.1126/science.7545954.

[13] Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, *et al*. Identification of the breast cancer susceptibility gene BRCA2. *Nature* 1995;378:789–792. https://doi.org/10.1038/378789a0.

[14] Foulkes WD. Inherited Susceptibility to Common Cancers. *New Engl J Med* 2008;359:2143–2153. https://doi.org/10.1056/NEJMra0802968.

[15] Armes JE, Trute L, White D, Southey MC, Hammet F, Tesoriero A, *et al*. Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2 mutation carriers: a population-based study. *Cancer Res* 1999;59:2011–2017.

[16] Armes JE, Venter DJ. The pathology of inherited breast cancer. *Pathology* 2002;34:309–314. https://doi.org/10.1080/00313020220147113.

[17] Mavaddat N, Dorling L, Carvalho S, Allen J, González-Neira A, Keeman R, *et al*. Pathology of Tumors Associated With Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. *JAMA Oncol* 2022;8:e216744. https://doi.org/10.1001/jamaoncol.2021.6744.

[18] Da Silva L, Lakhani SR. Pathology of hereditary breast cancer. *Mod Pathol* 2010;23:S46–S51. https://doi.org/10.1038/modpathol.2010.37.

[19] Evans DG, Lalloo F, Howell S, Verhoef S, Woodward ER, Howell A. Low prevalence of HER2 positivity amongst BRCA1 and BRCA2 mutation carriers and in primary BRCA screens. *Breast Cancer Res Treat* 2016;155:597–601. https://doi.org/10.1007/s10549-016-3697-z.

[20] Armes JE, Egan AJ, Southey MC, Dite GS, McCredie MR, Giles GG, *et al*. The histologic phenotypes of breast carcinoma occurring before age 40 years in women with and without BRCA1 or BRCA2 germline mutations: a population-based study. *Cancer* 1998;83:2335–2345.

[21] McCrorie AD, Ashfield S, Begley A, Mcilmunn C, Morrison PJ, Boyd C, *et al*. Multifocal breast cancers are more prevalent in *BRCA2* versus *BRCA1* mutation carriers. *J Pathol Clin Res* 2020;6:146–153. https://doi.org/10.1002/cjp2.155.

[22] Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2based on genetic testing in a Clinical Cancer Genetics service setting: Risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer* 2008;8:155. https://doi.org/10.1186/1471-2407-8-155.

[23] Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, *et al*. Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *Am J Hum Genet* 2003;72:1117–1130. https://doi.org/10.1086/375033.

[24] Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, *et al*. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* 1999;8:741–747.

[25] Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K-A, Mooij TM, Roos-Blom M-J, *et al*. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA* 2017;317:2402. https://doi.org/10.1001/jama.2017.7112.

[26] Liu M, Xie F, Liu M, Zhang Y, Wang S. Association between BRCA mutational status and survival in patients with breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2021;186:591–605. https://doi.org/10.1007/s10549-021-06104-y.

[27] Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, *et al*. Prospective Observational Study of Breast Cancer Treatment Outcomes for UK Women Aged 18–40 Years at Diagnosis: The POSH Study. *JNCI: J Natl Cancer Inst* 2013;105:978–988. https://doi.org/10.1093/jnci/djt134.

[28] Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, Altman DG, *et al*. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. *Lancet Oncol* 2018;19:169–180. https://doi.org/10.1016/S1470-2045(17)30891-4.

[29] Valachis A, Nearchou AD, Lind P. Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2014;144:443–455. https://doi.org/10.1007/s10549-014-2890-1.

[30] Maishman T, Cutress RI, Hernandez A, Gerty S, Copson EllenR, Durcan L, *et al*. Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer. *Ann Surg* 2017;266:165–172. https://doi.org/10.1097/SLA.0000000000001930.

[31] Shubeck S, Sevilimedu V, Berger E, Robson M, Heerdt AS, Pilewskie ML. Comparison of Outcomes Between BRCA Pathogenic Variant Carriers Undergoing Breast-Conserving Surgery Versus Mastectomy. *Ann Surg Oncol* 2022;29:4706–4713. https://doi.org/10.1245/s10434-022-11756-1.

[32] Pierce LJ, Phillips K-A, Griffith KA, Buys S, Gaffney DK, Moran MS, *et al*. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. *Breast Cancer Res Treat* 2010;121:389–398. https://doi.org/10.1007/s10549-010-0894-z.

[33] Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, *et al*. Cancer Risks for BRCA1 and BRCA2 Mutation Carriers: Results From Prospective Analysis of EMBRACE. *JNCI: J Natl Cancer Inst* 2013;105:812–822. https://doi.org/10.1093/jnci/djt095.

Please cite this article as: Cheah W et al., Clinical Impact of Constitutional Genomic Testing on Current Breast Cancer Care, Clinical Oncology, https://doi.org/10.1016/j.clon.2024.08.006

[34] Ain Q, Richardson C, Mutebi M, George A, Kemp Z, Rusby JE. Does mainstream BRCA testing affect surgical decision-making in newly-diagnosed breast cancer patients? *The Breast* 2023;67:30–35. https://doi.org/10.1016/j.breast.2022.12.001.

[35] Meiser B, Quinn VF, Mitchell G, Tucker K, Watts KJ, Rahman B, *et al*. Psychological outcomes and surgical decisions after genetic testing in women newly diagnosed with breast cancer with and without a family history. *Eur J Hum Genet* 2018;26:972–983. https://doi.org/10.1038/s41431-017-0057-3.

[36] Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, *et al*. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann Oncol* 2023;34:33–47. https://doi.org/10.1016/j.annonc.2022.10.004.

[37] Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, *et al*. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018;24:628–637. https://doi.org/10.1038/s41591-018-0009-7.

[38] Geyer CE, Sikov WM, Huober J, Rugo HS, Wolmark N, O'Shaughnessy J, *et al*. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. *Ann Oncol* 2022;33:384–394. https://doi.org/10.1016/j.annonc.2022.01.009.

[39] Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, *et al*. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021;32:1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019.

[40] Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, *et al*. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. *New Engl J Med* 2017;377:523–533. https://doi.org/10.1056/NEJMoa1706450.

[41] Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, *et al*. Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation. *New Engl J Med* 2018;379:753–763. https://doi.org/10.1056/NEJMoa1802905.

[42] Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, *et al*. Adjuvant Olaparib for Patients with *BRCA1* - or *BRCA2* -Mutated Breast Cancer. *New Engl J Med* 2021;384:2394–2405. https://doi.org/10.1056/NEJMoa2105215.

[43] *Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy* 2023https://wwwNiceOrgUk/Guidance/TA886.

[44] Nepomuceno T, De Gregoriis G, de Oliveira FMB, Suarez-Kurtz G, Monteiro A, Carvalho M. The Role of PALB2 in the DNA Damage Response and Cancer Predisposition. *Int J Mol Sci* 2017;18:1886. https://doi.org/10.3390/ijms18091886.

[45] Xia B, Dorsman JC, Ameziane N, de Vries Y, Rooimans MA, Sheng Q, *et al*. Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. *Nat Genet* 2007;39:159–161. https://doi.org/10.1038/ng1942.

[46] Rahman N, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, *et al*. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007;39:165–167. https://doi.org/10.1038/ng1959.

[47] Hamdan O, Nowak KM. Gene of the month: PALB2. *J Clin Pathol* 2023;76:73–75. https://doi.org/10.1136/jcp-2022-208461.

[48] Dorling L, Carvalho S, Allen J, Parsons MT, Fortuno C, González-Neira A, *et al*. Breast cancer risks associated with missense variants in breast cancer susceptibility genes. *Genome Med* 2022;14:51. https://doi.org/10.1186/s13073-022-01052-8.

[49] Southey M, Teo Winship I. PALB2 and breast cancer: ready for clinical translation. *Appl Clin Genet* 2013;43. https://doi.org/10.2147/TACG.S34116.

[50] Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, *et al*. Breast-Cancer Risk in Families with Mutations in *PALB2*. *New Engl J Med* 2014;371:497–506. https://doi.org/10.1056/NEJMoa1400382.

[51] Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, *et al*. Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families. *J Clin Oncol* 2020;38:674–685. https://doi.org/10.1200/JCO.19.01907.

[52] Deng M, Chen H, Zhu X, Luo M, Zhang K, Xu C, *et al*. Prevalence and clinical outcomes of germline mutations in *BRCA1/2* and *PALB2* genes in 2769 unselected breast cancer patients in China. *Int J Cancer* 2019;145:1517–1528. https://doi.org/10.1002/ijc.32184.

[53] Yadav S, Boddicker NJ, Na J, Polley EC, Hu C, Hart SN, *et al*. Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in *ATM* , *BRCA1* , *BRCA2* , *CHEK2* , and *PALB2*. *J Clin Oncol* 2023;41:1703–1713. https://doi.org/10.1200/JCO.22.01239.

[54] de Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, *et al*. Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline *BRCA1/2* Mutations and Selected Sporadic Cancers. *Cancer Discov* 2017;7:620–629. https://doi.org/10.1158/2159-8290.CD-16-1250.

[55] Isaac D, Karapetyan L, Tamkus D. Association of Germline *PALB2* Mutation and Response to Platinum-Based Chemotherapy in Metastatic Breast Cancer: A Case Series. *JCO Precis Oncol* 2018;1–5. https://doi.org/10.1200/PO.17.00258.

[56] Magni M, Ruscica V, Buscemi G, Kim J-E, Nachimuthu BT, Fontanella E, *et al*. Chk2 and REGγ-dependent DBC1 regulation in DNA damage induced apoptosis. *Nucleic Acids Res* 2014;42:13150–13160. https://doi.org/10.1093/nar/gku1065.

[57] Schutte M, Seal S, Barfoot R, Meijers-Heijboer H, Wasielewski M, Evans DG, *et al*. Variants in CHEK2 Other than 1100delC Do Not Make a Major Contribution to Breast Cancer Susceptibility. *Am J Hum Genet* 2003;72:1023–1028. https://doi.org/10.1086/373965.

[58] Bychkovsky BL, Agaoglu NB, Horton C, Zhou J, Yussuf A, Hemyari P, *et al*. Differences in Cancer Phenotypes Among Frequent *CHEK2* Variants and Implications for Clinical Care—Checking *CHEK2*. *JAMA Oncol* 2022;8:1598. https://doi.org/10.1001/jamaoncol.2022.4071.

[59] Muranen TA, Blomqvist C, Dörk T, Jakubowska A, Heikkilä P, Fagerholm R, *et al*. Patient survival and tumor characteristics associated with CHEK2:p.I157T – findings from the Breast Cancer Association Consortium. *Breast Cancer Res* 2016;18:98. https://doi.org/10.1186/s13058-016-0758-5.

[60] Adank MA, Jonker MA, Kluijt I, van Mil SE, Oldenburg RA, Mooi WJ, *et al*. CHEK2*1100delC homozygosity is associated with a high breast cancer risk in women. *J Med Genet* 2011;48:860–863. https://doi.org/10.1136/jmedgenet-2011-100380.

[61] Weischer M, Bojesen SE, Ellervik C, Tybjærg-Hansen A, Nordestgaard BG. *CHEK2* *1100delC Genotyping for Clinical Assessment of Breast Cancer Risk: Meta-Analyses of 26,000 Patient Cases and 27,000 Controls. *J Clin Oncol* 2008;26:542–548. https://doi.org/10.1200/JCO.2007.12.5922.

Please cite this article as: Cheah W et al., Clinical Impact of Constitutional Genomic Testing on Current Breast Cancer Care, Clinical Oncology, https://doi.org/10.1016/j.clon.2024.08.006

[62] Greville-Heygate SL, Maishman T, Tapper WJ, Cutress RI, Copson E, Dunning AM, *et al*. Pathogenic Variants in *CHEK2* Are Associated With an Adverse Prognosis in Symptomatic Early-Onset Breast Cancer. *JCO Precis Oncol* 2020:472–485. https://doi.org/10.1200/PO.19.00178.

[63] Schmidt MK, Hogervorst F, van Hien R, Cornelissen S, Broeks A, Adank MA, *et al*. Age- and Tumor Subtype–Specific Breast Cancer Risk Estimates for *CH EK 2* *1100delC Carriers. *J Clin Oncol* 2016;34:2750–2760. https://doi.org/10.1200/JCO.2016.66.5844.

[64] Weischer M, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, van't Veer LJ, *et al*. *CHEK2* *1100delC Heterozygosity in Women With Breast Cancer Associated With Early Death, Breast Cancer–Specific Death, and Increased Risk of a Second Breast Cancer. *J Clin Oncol* 2012;30:4308–4316. https://doi.org/10.1200/JCO.2012.42.7336.

[65] Akdeniz D, Schmidt MK, Seynaeve CM, McCool D, Giardiello D, van den Broek AJ, *et al*. Risk factors for metachronous contralateral breast cancer: A systematic review and meta-analysis. *The Breast* 2019;44:1–14. https://doi.org/10.1016/j.breast.2018.11.005.

[66] Morra A, Schreurs MAC, Andrulis IL, Anton-Culver H, Augustinsson A, Beckmann MW, *et al*. Association of the *CHEK2* c. 1100delC variant, radiotherapy, and systemic treatment with contralateral breast cancer risk and breast cancer-specific survival. *Cancer Med* 2023;12:16142–16162. https://doi.org/10.1002/cam4.6272.

[67] Meyer A, Dörk T, Sohn C, Karstens JH, Bremer M. Breast cancer in patients carrying a germ-line CHEK2 mutation: Outcome after breast conserving surgery and adjuvant radiotherapy. *Radiother Oncol* 2007;82:349–353. https://doi.org/10.1016/j.radonc.2006.12.002.

[68] Broeks A, de Witte L, Nooijen A, Huseinovic A, Klijn JGM, van Leeuwen FE, *et al*. Excess Risk for Contralateral Breast Cancer in CHEK2*1100delC Germline Mutation Carriers. *Breast Cancer Res Treat* 2004;83:91–93. https://doi.org/10.1023/B:BREA.0000010697.49896.03.

[69] Kriege M, Jager A, Hollestelle A, Berns EMJJ, Blom J, Meijer-van Gelder ME, *et al*. Sensitivity to systemic therapy for metastatic breast cancer in CHEK2 1100delC mutation carriers. *J Cancer Res Clin Oncol* 2015;141:1879–1887. https://doi.org/10.1007/s00432-015-1981-7.

[70] Kriege M, Hollestelle A, Jager A, Huijts PEA, Berns EM, Sieuwerts AM, *et al*. Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy. *Br J Cancer* 2014;111:1004–1013. https://doi.org/10.1038/bjc.2014.306.

[71] Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, *et al*. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol* 2020;38:4274–4282. https://doi.org/10.1200/JCO.20.02151.

[72] Prokopcova J, Kleibl Z, Banwell CM, Pohlreich P. The role of ATM in breast cancer development. *Breast Cancer Res Treat* 2007;104:121–128. https://doi.org/10.1007/s10549-006-9406-6.

[73] Vega A. Breast cancer genes: beyond BRCA1 and BRCA2. *Front Biosci* 2013;18:1358. https://doi.org/10.2741/4185.

[74] Decker B, Allen J, Luccarini C, Pooley KA, Shah M, Bolla MK, *et al*. Rare, protein-truncating variants in *ATM* , *CHEK2* and *PALB2* , but not *XRCC2* , are associated with increased breast cancer risks. *J Med Genet* 2017;54:732–741. https://doi.org/10.1136/jmedgenet-2017-104588.

[75] Southey MC, Goldgar DE, Winqvist R, Pylkäs K, Couch F, Tischkowitz M, *et al*. *PALB2* , *CHEK2* and *ATM* rare variants and cancer risk: data from COGS. *J Med Genet* 2016;53:800–811. https://doi.org/10.1136/jmedgenet-2016-103839.

[76] Hall MJ, Bernhisel R, Hughes E, Larson K, Rosenthal ET, Singh NA, *et al*. Germline Pathogenic Variants in the Ataxia Telangiectasia Mutated (*ATM*) Gene are Associated with High and Moderate Risks for Multiple Cancers. *Cancer Prev Res* 2021;14:433–440. https://doi.org/10.1158/1940-6207.CAPR-20-0448.

[77] Reiner AS, Robson ME, Mellemkjær L, Tischkowitz M, John EM, Lynch CF, *et al*. Radiation Treatment, *ATM* , *BRCA1/2* , and *CHEK2* *1100delC Pathogenic Variants and Risk of Contralateral Breast Cancer. *JNCI: J Natl Cancer Inst* 2020;112:1275–1279. https://doi.org/10.1093/jnci/djaa031.

[78] Modlin LA, Flynn J, Zhang Z, Cahlon O, Mueller B, Khan AJ, *et al*. Tolerability of Breast Radiotherapy Among Carriers of *ATM* Germline Variants. *JCO Precis Oncol* 2021:227–234. https://doi.org/10.1200/PO.20.00334.

[79] Goel V, Sharma D, Sharma A, Mallick S. A systematic review exploring the role of modern radiation for the treatment of Hereditary or Familial Breast Cancer. *Radiother Oncol* 2022;176:59–67. https://doi.org/10.1016/j.radonc.2022.09.007.

[80] Bruno L, Ostinelli A, Waisberg F, Enrico D, Ponce C, Rivero S, *et al*. Cyclin-Dependent Kinase 4/6 Inhibitor Outcomes in Patients With Advanced Breast Cancer Carrying Germline Pathogenic Variants in DNA Repair–Related Genes. *JCO Precis Oncol* 2022. https://doi.org/10.1200/PO.21.00140.

[81] Baumann P, West SC. Role of the human RAD51 protein in homologous recombination and double-stranded-break repair. *Trends Biochem Sci* 1998;23:247–251. https://doi.org/10.1016/S0968-0004(98)01232-8.

[82] Dorling L, Carvalho S, Allen J, González-Neira A, Luccarini C, Wahlström C, *et al*. Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women. *New Engl J Med* 2021;384:428–439. https://doi.org/10.1056/NEJMoa1913948.

[83] Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, *et al*. A Population-Based Study of Genes Previously Implicated in Breast Cancer. *New Engl J Med* 2021;384:440–451. https://doi.org/10.1056/NEJMoa2005936.

[84] Hanson H, Kulkarni A, Loong L, Kavanaugh G, Torr B, Allen S, *et al*. UK consensus recommendations for clinical management of cancer risk for women with germline pathogenic variants in cancer predisposition genes: *RAD51C* , *RAD51D* , *BRIP1* and *PALB2*. *J Med Genet* 2023;60:417–429. https://doi.org/10.1136/jmg-2022-108898.

[85] Chen X, Li Y, Ouyang T, Li J, Wang T, Fan Z, *et al*. Associations between RAD51D germline mutations and breast cancer risk and survival in BRCA1/2-negative breast cancers. *Ann Oncol* 2018;29:2046–2051. https://doi.org/10.1093/annonc/mdy338.

[86] UKCGG Management Guidelines for RAD51C/D germline pathogenic variant carriers n.d, https://www.ukcgg.org/information-education/ukcgg-leaflets-and-guidelines/. [Accessed 8 August 2023].

[87] Haffty BG, Euhus DM, Pierce LJ. Genetic Factors in the Locoregional Management of Breast Cancer. *J Clin Oncol* 2020;38:2220–2229. https://doi.org/10.1200/JCO.19.02859.

[88] McCabe N, Turner NC, Lord CJ, Kluzek K, Białkowska A, Swift S, *et al*. Deficiency in the Repair of DNA Damage by Homologous Recombination and Sensitivity to Poly(ADP-Ribose) Polymerase Inhibition. *Cancer Res* 2006;66:8109–8115. https://doi.org/10.1158/0008-5472.CAN-06-0140.

[89] Riley T, Sontag E, Chen P, Levine A. Transcriptional control of human p53-regulated genes. *Nat Rev Mol Cell Biol* 2008;9:402–412. https://doi.org/10.1038/nrm2395.

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[90] Malkin D, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH, *et al*. Germ Line p53 Mutations in a Familial Syndrome of Breast Cancer, Sarcomas, and Other Neoplasms. *Science (1979)* 1990;250:1233–1238. https://doi.org/10.1126/science.1978757.

[91] Nichols KE, Malkin D, Garber JE, Fraumeni JF, Li FP. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. *Cancer Epidemiol Biomarkers Prev* 2001;10:83–87.

[92] Levine AJ. Spontaneous and inherited TP53 genetic alterations. *Oncogene* 2021;40:5975–5983. https://doi.org/10.1038/s41388-021-01991-3.

[93] Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, *et al*. Risks of first and subsequent cancers among *TP53* mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer* 2016;122:3673–3681. https://doi.org/10.1002/cncr.30248.

[94] Wilson JRF, Bateman AC, Hanson H, An Q, Evans G, Rahman N, *et al*. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. *J Med Genet* 2010;47:771–774. https://doi.org/10.1136/jmg.2010.078113.

[95] Sheng S, Xu Y, Guo Y, Yao L, Hu L, Ouyang T, *et al*. Prevalence and clinical impact of *TP53* germline mutations in Chinese women with breast cancer. *Int J Cancer* 2020;146:487–495. https://doi.org/10.1002/ijc.32424.

[96] Guo Y, Wan Q, Ouyang T, Li J, Wang T, Fan Z, *et al*. Risk of ipsilateral breast tumor recurrence and contralateral breast cancer in patients with and without TP53 variant in a large series of breast cancer patients. *The Breast* 2022;65:55–60. https://doi.org/10.1016/j.breast.2022.07.002.

[97] Hyder Z, Harkness EF, Woodward ER, Bowers NL, Pereira M, Wallace AJ, *et al*. Risk of Contralateral Breast Cancer in Women with and without Pathogenic Variants in BRCA1, BRCA2, and TP53 Genes in Women with Very Early-Onset (<36 Years) Breast Cancer. *Cancers (Basel)* 2020;12:378. https://doi.org/10.3390/cancers12020378.

[98] Heymann S, Delaloge S, Rahal A, Caron O, Frebourg T, Barreau L, *et al*. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. *Radiat Oncol* 2010;5:104. https://doi.org/10.1186/1748-717X-5-104.

[99] Petry V, Bonadio RC, Cagnacci AQC, Senna LAL, Campos R do NG, Cotti GC, *et al*. Radiotherapy-induced malignancies in breast cancer patients with TP53 pathogenic germline variants (Li–Fraumeni syndrome). *Fam Cancer* 2020;19:47–53. https://doi.org/10.1007/s10689-019-00153-5.

[100] Nandikolla A, Venugopal S, Anampa J. Breast cancer in patients with Li–Fraumeni syndrome – a case-series study and review of literature. *Breast Cancer Targets Ther* 2017;9. https://doi.org/10.2147/BCTT.S134241. 207–15.

[101] Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, *et al*. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann Oncol* 2023;34:33–47. https://doi.org/10.1016/j.annonc.2022.10.004.

[102] Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG. Guidelines for the Li–Fraumeni and heritable TP53-related cancer syndromes. *Eur J Hum Genet* 2020;28:1379–1386. https://doi.org/10.1038/s41431-020-0638-4.

[103] Kasper E, Angot E, Colasse E, Nicol L, Sabourin J-C, Adriouch S, *et al*. Contribution of genotoxic anticancer treatments to the development of multiple primary tumors in the context of germline TP53 mutations. *Eur J Cancer* 2018;101:254–262. https://doi.org/10.1016/j.ejca.2018.06.011.

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