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REVIEW

Hereditary breast cancer: syndromes, tumour pathology and molecular testing

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Hereditary breast cancer: syndromes, tumour pathology and molecular testing

Hereditary factors account for a significant proportion of breast cancer risk. Approximately 20% of hereditary breast cancers are attributable to pathogenic variants in the highly penetrant *BRCA1* and *BRCA2* genes. A proportion of the genetic risk is also explained by pathogenic variants in other breast cancer susceptibility genes, including *ATM*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D* and *BARD1*, as well as genes associated with breast cancer predisposition syndromes – *TP53* (Li–Fraumeni syndrome), *PTEN* (Cowden syndrome), *CDH1* (hereditary diffuse gastric cancer), *STK11* (Peutz–Jeghers syndrome) and *NF1* (neurofibromatosis type 1). Polygenic risk, the cumulative risk from carrying multiple low-penetrance breast cancer susceptibility alleles, is also a well-recognised contributor to risk. This review provides an overview of the established breast cancer susceptibility genes as well as breast cancer predisposition syndromes, highlights distinct genotype–phenotype correlations associated with germline mutation status and discusses molecular testing and therapeutic implications in the context of hereditary breast cancer.

Keywords: familial breast cancer, BRCA1, BRCA2, cancer syndromes, genotype–phenotype correlation

Introduction

Breast cancer is the leading cause of cancer death in women worldwide.[1] While most breast cancers are sporadic, approximately 5–10% are hereditary.[2] Pathogenic variants in the high-penetrance genes *BRCA1* and *BRCA2* account for approximately 20% of heritable breast cancer risk.[3,4] *BRCA1* and *BRCA2* play an integral role in DNA damage repair by homologous recombination (HR), and germline variants in several other HR repair genes are also implicated in hereditary breast cancer risk, including *CHEK2*, *PALB2*, *ATM*, *RAD51C*, *RAD51D* and *BARD1*.[5–7] An additional proportion of patients with hereditary breast cancer have germline variants in genes associated with recognised cancer susceptibility syndromes, including *TP53* (Li–Fraumeni syndrome), *PTEN* (Cowden syndrome), *STK11* (Peutz–Jeghers syndrome), *CDH1* (hereditary diffuse gastric cancer and hereditary lobular breast cancer) and *NF1* (neurofibromatosis type 1).[8] An association between mutations in mismatch repair (MMR) genes (Lynch syndrome) and breast cancer has not been conclusively established. Furthermore, a substantial proportion of hereditary breast cancer risk is not explained by pathogenic variants in specific genes but is partly attributable to polygenic risk, referring to variable combinations of multiple low-penetrance breast cancer susceptibility alleles.[9] Characteristic histopathological features and immunohistochemical phenotypes have been associated with germline variants in several breast cancer susceptibility genes. Recognition of these pathological features, together with known risk factors such as age and family history, informs patient risk prediction, guides genetic testing and facilitates the diagnosis of hereditary breast cancer,

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which influences patient management and surveillance. In this review we provide an overview of the established breast cancer susceptibility genes and syndromes, with an emphasis on distinct pathological and molecular associations and their clinical implications.

Historical background

A hereditary component to breast cancer predisposition was first proposed by the French surgeon, Pierre Paul Broca in 1866, when he described a familial cluster of breast cancer cases affecting multiple women across four generations.[10] Subsequent epidemiological studies firmly established family history as a major risk factor for developing breast cancer,[11–13] with the magnitude of risk further increased by the number of affected relatives, closer degree of relationship and younger age at diagnosis.[13,14] In 1988, segregation analysis of 1579 high-risk breast cancer families with multiple affected individuals found that disease clustering was fully explained by an autosomal-dominant model of transmission with a highly penetrant susceptibility allele.[15] Two years later, linkage studies revealed that the locus of the gene for early-onset familial breast cancer was on chromosome 17.[16] In 1994, *BRCA1* was discovered to be the causative gene at this locus.[17] In 1995, *BRCA2* was identified as the second breast cancer susceptibility gene and localised to chromosome 13.[18,19] In 1997 the Breast Cancer Linkage Consortium reported distinct pathological characteristics of *BRCA1/2*-associated familial breast cancers compared to sporadic cases,[20] and key histological phenotypes associated with *BRCA1/2* mutations were described in 1998.[21]

Research into rare syndromes with a high incidence of breast cancer led to the recognition of several additional moderate- and high-penetrance genes that contribute to hereditary breast cancer risk, including *TP53*,[22] *CDH1*,[23] *PTEN*,[24] *STK11*[25] and *NF1*.[26] Studies of non-*BRCA1/2* familial breast cancer patients implicated germline variants in multiple genes involved in DNA damage repair, including *ATM*,[27] *CHEK2*,[28] *PALB2*,[29] *BARD1*,[30] *RAD51C*[31] and *RAD51D*[32] in breast cancer susceptibility. In 2007, the first breast cancer genome-wide association studies (GWAS) were published,[33–35] identifying several common low-penetrance variants associated with genetic breast cancer risk, while the implementation of next-generation sequencing (NGS) approaches in population-based studies has defined rare genomic risk variants and quantified the magnitude of their associated risk.[6,7] Known germline variants in established high-, moderate- and low-penetrance genes collectively explain approximately 50% of familial breast cancer risk.[36] Ongoing research into the genetic basis of familial breast cancer will probably uncover novel risk variants, further elucidate the role of susceptibility genes in breast cancer aetiology and clarify how genetic factors interact with other risk factors, thereby improving individual risk prediction.

Heritable breast cancer risk

The genetic basis of breast cancer predisposition is a rapidly evolving topic and this is reflected in the substantially revised 'genetic tumour syndromes of the breast' chapter in the fifth edition of the World Health Organisation (WHO) classification of tumours of the breast (2019),[37] which incorporates a growing number of susceptibility genes and predisposition syndromes implicated in breast cancer risk (Table 1). The established and emerging breast cancer susceptibility genes and predisposition syndromes are summarised below.

BREAST CANCER PREDISPOSITION SYNDROMES

Hereditary breast and ovarian cancer syndrome

Hereditary breast and ovarian cancer syndrome is associated with germline mutations in the tumour suppressor genes *BRCA1* and *BRCA2* and is inherited in an autosomal-dominant manner. *BRCA1* and *BRCA2* encode for BRCA1/2 proteins involved in the repair of double-strand DNA breaks through HR.[38,39] Pathogenic variants in *BRCA1/2* are highly penetrant and are associated with a significantly elevated lifetime risk of breast and ovarian cancer[40–42] and increased susceptibility to a number of other malignancies, particularly prostate (*BRCA1/2*) and pancreatic cancer (*BRCA2*).[43–46] In a large prospective cohort, the cumulative risk of breast cancer up to age 80 years was 72% for *BRCA1* and 69% for *BRCA2* mutation carriers.[41] In addition, *BRCA1* and *BRCA2* mutation carriers have an increased risk of contralateral breast cancer (40 and 26%, respectively),[41] and germline mutations in *BRCA2* are associated with male breast cancer.[47,48]

Li–Fraumeni syndrome

Li–Fraumeni syndrome is an autosomal-dominant syndrome associated with germline mutations in the tumour suppressor gene *TP53*.[22] *TP53* encodes the

Table 1. Comparison of the topics included in the 'genetic susceptibility: inherited syndromes' chapter in the WHO classification, 4th edition (2012) and the 'genetic tumour syndromes of the breast' chapter in the WHO classification, 5th edition (2019). Of note, the association between Lynch syndrome and breast cancer is controversial, so the editorial board did not feel that there was sufficient evidence to include Lynch syndrome in the 2019 classification system. In the current classification system, Li–Fraumeni syndrome has also been split into two categories associated with variants in either *TP53* or *CHEK2*. These classification systems may continue to evolve as more knowledge is accrued

WHO classification 4th edition (2012)[199]	WHO classification 5th edition (2019)[37]
BRCA1 and BRCA2 syndromes	BRCA1/2-associated hereditary breast and ovarian cancer syndrome
Li–Fraumeni syndrome	Li–Fraumeni syndrome, TP53-associated
	Li–Fraumeni syndrome, CHEK2-associated
Ataxia–telangiectasia	Ataxia–telangiectasia
Cowden syndrome	Cowden syndrome
Lynch syndrome	Not included in new edition
Other breast cancer-predisposing genes	CDH1-associated breast cancer
	PALB2-associated cancers
	Peutz–Jeghers syndrome
	Neurofibromatosis type 1
	The polygenic component of breast cancer susceptibility

protein p53, an important cell cycle regulator.[49,50] Germline mutations in *TP53* are associated with an increased risk of early onset malignancy, including epithelial, mesenchymal and haematological malignancies.[51–54] Breast cancer is the most common epithelial malignancy in women,[55] with an 85% cumulative lifetime risk of breast cancer by age 60 years.[56] The median age of breast cancer diagnosis is 34 years[57] and germline *TP53* mutations are identified in approximately 5–8% of women diagnosed with breast cancer before the age of 30 years.[58]

Cowden syndrome

Cowden syndrome is an autosomal-dominant syndrome associated with germline mutations in the tumour suppressor gene *PTEN*[24] and is the most common disorder in the PTEN hamartoma tumour syndrome spectrum.[59] The clinical manifestations of Cowden syndrome include the development of multiple hamartomas as well as an elevated risk of breast, thyroid, endometrial, renal and colorectal malignancies.[60,61] Breast cancer is the most common malignancy in Cowden syndrome, with an estimated lifetime risk of up to 85%[62,63] and an average age of diagnosis between 38 and 46 years.[64]

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is an autosomal-dominant syndrome attributable to mutations in the tumour suppressor gene *STK11*.[65] Peuts–Jeghers syndrome is characterised by the development of mucocutaneous pigmentation, hamartomatous gastrointestinal polyps and is associated with an increased risk of gastrointestinal, breast, lung, gynaecological and genitourinary malignancies.[66-70] Breast cancer is the second most common malignancy after gastrointestinal tumours, with a cumulative breast cancer risk of up to 54% at age 64 years and a mean age at diagnosis of 37 years.[67]

Hereditary diffuse gastric cancer and hereditary lobular breast cancer

Hereditary diffuse gastric cancer (HDGC) and hereditary lobular breast cancer (HLBC) are autosomal-dominant syndromes associated with inactivating germline mutations in *CDH1*.[71] *CDH1* encodes E-cadherin, a transmembrane protein involved in cell-to-cell adhesion.[72] Both men and women with HDGC have an elevated lifetime risk of developing diffuse gastric cancer (70 and 56% by age 80 years, respectively)[73] and women also have a 42% lifetime risk of developing invasive lobular carcinoma (ILC).[73,74] ILC can be the first manifestation of HDGC, presenting as bilateral disease in women younger than 50 years of age.[75] HLBC includes families with germline *CDH1* mutations who show a predisposition to ILC but do not have a family history of gastric cancer.[76–78] However, even without a family history of gastric cancer, patients with HLBC have a markedly elevated risk of developing occult gastric malignancy.[79] Breast cancer metastasis may need to be excluded in patients with diffuse gastric cancer who also have a history of ILC, as ILC is the most common breast cancer subtype to metastasise to the stomach and morphologically mimics diffuse-type gastric cancer.[80] Differentiating metastatic breast from primary gastric carcinoma requires a panel of immunohistochemical markers; for example, GATA binding protein 3 (GATA3), oestrogen receptor (ER) and progesterone receptor (PR) positivity supports breast origin, while CK20 and CDX2 positivity is seen in a proportion of gastric carcinomas.[81,82]

Neurofibromatosis type 1

Neurofibromatosis type 1 is associated with mutations in the tumour suppressor gene *NF1*,[83] which may be inherited in an autosomal-dominant manner or occur sporadically in approximately half the cases.[84] Clinical manifestations include neurocutaneous lesions and an increased risk of malignancy, predominantly involving the nervous system and breast.[85] Women with neurofibromatosis type 1 have an increased risk of early-onset breast cancer, with a four to 11-fold increase in breast cancer risk up to the age of 50 years[84] and a 17% cumulative lifetime risk of breast cancer by age 70 years.[86]

Lynch syndrome

Lynch syndrome is an autosomal-dominant syndrome primarily attributable to germline mutations in the MMR genes *MLH1*, *MSH2*, *MSH6* and *PMS2*.[87] The most common malignancies in Lynch syndrome involve the colon, endometrium, ovaries and stomach.[88,89] An association between Lynch syndrome and breast cancer has not been definitively established. Some studies have reported an increased risk of breast cancer[90–92] and a prospective cohort study of MMR gene mutation carriers identified a fourfold increase in breast cancer risk with a median follow-up of 5 years.[88] However, data from the Prospective Lynch Syndrome Database showed that the risk of developing breast cancer in carriers of *MLH1*, *MSH2* and *MSH6* pathogenic germline variants was not significantly elevated among the general population.[89,93,94] In addition, microsatellite instability (MSI) as a result of MMR deficiency is uncommon in breast cancer and seen in fewer than 2% of cases.[95] In a cohort of 640 breast cancers, only 11 were found to have MMR deficiency using whole genome sequencing and more than 80% of the MMR-deficient tumours did not have Lynch syndrome.[95] Furthermore, analysis of breast carcinomas arising in patients with Lynch syndrome found that only 51% of tumours demonstrated evidence of MMR deficiency on immunohistochemistry,[96] suggesting that half the cases had a different aetiology.

HOMOLOGOUS RECOMBINATION DEFICIENCY AND BREAST CANCER RISK

HR is a high-fidelity DNA repair pathway utilised in the repair of double-strand DNA breaks.[97,98] A defect in HR is termed homologous recombination deficiency (HRD) and is characterised by defective DNA repair, genomic instability and cancer predisposition.[99] In addition to *BRCA1/2*, several other genes involved in the HR repair pathway are associated with an increased risk of breast cancer, including *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D* and *BARD1*. Two recently published population-based case–control studies BRIDGES[6] and CARRIERS[7] assessed sequencing data from almost 180 000 women, including unselected breast cancer patients as well as controls (unaffected individuals), to determine the prevalence of pathogenic variants in breast cancer predisposition genes in the general population and their associated breast cancer risk. Both studies identified an elevated breast cancer risk in women with germline pathogenic variants in eight genes involved in the HR repair pathway: *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D* and *BARD1*. Germline pathogenic variants in these genes, together with *CDH1*, *NF1*, *PTEN* and *TP53*, were detected in 5.03% of unselected breast cancer cases compared to 1.63% of controls.[7]

PALB2

Partner and localiser of BRCA2 *(PALB2)* is a tumour suppressor gene involved in the HR repair pathway through its interaction with BRCA2.[100–102] Bi-allelic germline *PALB2* mutations are associated with Fanconi anaemia and a predisposition to childhood malignancies,[103] whereas mono-allelic germline mutations confer an increased risk of breast, pancreatic and ovarian cancer.[29,104–108] Mono-allelic germline *PALB2* mutations are identified in up to ~5% of patients with hereditary breast cancer[104,109] and female *PALB2* mutation carriers have a 2.3 to ninefold increased risk of breast cancer,[29,107] with an estimated cumulative lifetime risk of 35% by age 70 years.[107]

ATM

Ataxia–telangiectasia-mutated (*ATM*) gene is a tumour suppressor gene that encodes a serine/threonine protein kinase involved in the HR repair pathway, regulation of cell-cycle check-points and intracellular signalling pathways.[110] Bi-allelic loss of function variants in *ATM* are associated with the development of ataxia–telangiectasia – a rare autosomal recessive neurodegenerative disorder – and confer increased cancer susceptibility.[27,111,112] Heterozygous carriers have a threefold increased risk of breast cancer and the risk is reported as sevenfold for women younger than 55 years.[112] The estimated cumulative lifetime risk of breast cancer in heterozygous mutation carriers is ~33% by age 80 years.[113]

CHEK2

Check-point kinase 2 (*CHEK2*) tumour suppressor gene encodes CHK2, a serine/threonine protein kinase involved in the HR repair pathway, cell cycle arrest and apoptosis in response to DNA damage.[114] Germline *CHEK2* mutations are associated with an increased risk of breast, prostate, kidney, colon,

thyroid and gastric cancer as well as sarcoma and non-Hodgkin lymphoma,[115–118] in some cases manifesting in a Li–Fraumeni-like phenotype (referred to as CHEK2-associated Li–Fraumeni syndrome or Li–Fraumeni syndrome 2).[119] Pathogenic variants in *CHEK2* are associated with a moderate breast cancer risk, with an odds ratio of 2.47 [95% confidence interval (CI) = 2.02–3.05][7] The estimated lifetime breast cancer risk is 21% by age 70 years,[120] and the magnitude of this risk as much as doubles when both first- and second-degree relatives have a history of breast cancer.[120,121]

RAD51C, *RAD51D* and *BARD1*

RAD51C, *RAD51D* and *BARD1* are tumour suppressor genes involved in the HR repair pathway and cell cycle progression.[122] Pathogenic variants in *BARD1*, *RAD51C* and *RAD51D* show a modest association with overall breast cancer risk, with reported odds ratios of 2.09 (95% CI = 1.35–3.23), 1.93 (95% CI = 1.20–3.11) and 1.80 (95% CI = 1.11–2.93), respectively;[6] however, demonstrate a stronger association (odds ratios > 2) with ER-negative and triple-negative disease.[7] Carriers of protein-truncating mutations in these genes are estimated to have a moderate absolute breast cancer risk (17–30%) by age 80 years.[6]

POLYGENIC RISK

Pathogenic variants in moderate- and high-penetrance susceptibility genes explain approximately 25–30% of heritable breast cancer risk.[123] A further 18% is attributable to polygenic risk, pertaining to variable combinations of hundreds of common low-penetrance breast cancer susceptibility alleles, identified using population-based GWAS.[9,124,125] These low-penetrance genetic variants are often located in non-coding regions of DNA and individually confer a small risk of breast cancer (odds ratio < 1.5).[124,126] However, the magnitude of breast cancer risk can be substantial when the sum of individual risk is assessed, expressed as the polygenic risk score.[127] For women in the top centile of the polygenic risk score based on 313 confirmed risk loci, there was a ~ 33% lifetime risk of breast cancer, with a fourfold increased risk of developing ER-positive breast cancer compared to women in the middle quintile.[9]

Tumour pathology

HISTOPATHOLOGY

Invasive carcinoma of no special type (IC-NST) is the most common histological tumour subtype in hereditary breast cancer. *BRCA1*-associated breast carcinomas are typically high-grade and characteristically exhibit medullary pattern features, including a pushing margin, solid growth, necrosis and prominent lymphocytic infiltrate (Figure 1A);[21,128] however, low-grade subtypes such as tubular carcinoma can rarely be seen.[129] *BRCA2*-associated breast cancers are more heterogenous in terms of grade and spectrum of histological tumour subtypes,[130–132] with a larger proportion of tumours being low- and intermediate-grade compared to *BRCA1*-associated cancers. Germline *CDH1* mutations are specifically associated with ILC (Figure 1B);[23,133] however, rare cases of IC-NST have been described in *CDH1* mutation carriers.[134] Distinct genotype–phenotype correlations are less well defined for other breast cancer risk genes. Most breast carcinomas described in the context of Li–Fraumeni syndrome[135] and neurofibromatosis type 1[136] as well as germline *PALB2*[137] and *ATM*[138] mutations are high-grade IC-NST. Tumours arising in *PALB2* mutation carriers were also associated with minimal sclerosis, and this was reported to be predictive of *PALB2* mutation status.[137] Breast carcinomas with MMR deficiency are typically high-grade and are significantly more likely to show solid growth, necrosis, increased mitotic activity and a prominent lymphocytic infiltrate.[96] In contrast, breast carcinomas in Cowden syndrome are more commonly low- and intermediate-grade IC-NST,[139,140] with a proportion of cases exhibiting apocrine differentiation (Figure 1C).[141] Germline *CHEK2*-associated breast cancer can be of any grade; the most prevalent c.1100delC variant is associated with IC-NST,[142–144] while p.I157T carrier tumours show an association with lobular differentiation.[145,146] The polygenic risk score may also convey subtype-specific risks; for example, an ILC-specific predisposition polymorphism has been identified at 7q34 (rs11977670).[147]

IMMUNOHISTOCHEMICAL PHENOTYPES AND INTRINSIC BREAST CANCER SUBTYPES

Triple-negative

BRCA1-associated breast cancers are more likely to be ER-, PR- and human epidermal growth factor receptor 2 (HER2)-negative ('triple-negative')[5,148,149] and the majority show a 'basal' phenotype (expression of high molecular weight cytokeratins such as CK5/6 and CK14 on immunohistochemistry).[150–152] Indeed, more than 60% of tumours arising in the context of *BRCA1* mutations are triple-negative[5,130,131] and a triple-negative phenotype is highly predictive of *BRCA1* mutation status.[153]

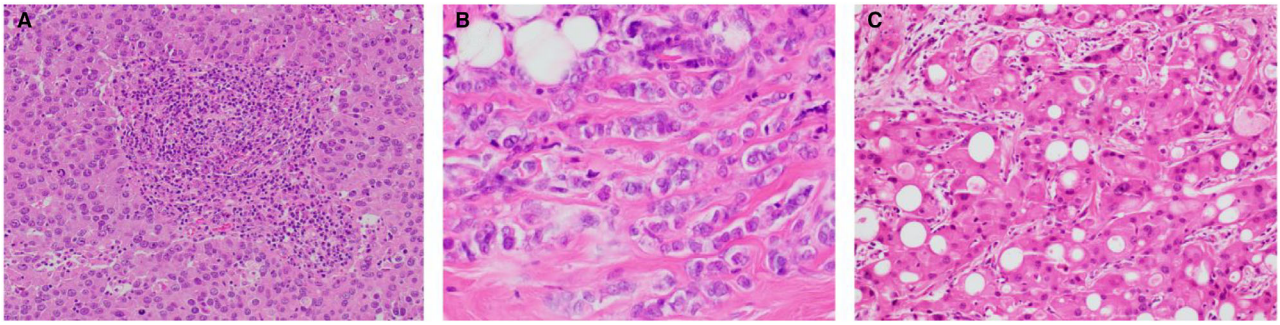

Figure 1. Examples of tumour pathology in hereditary breast cancer. **A,** *BRCA1*-associated invasive carcinoma of no special type with medullary pattern; **B,** *CDH1*-associated breast cancer is characteristically invasive lobular carcinoma; **C,** invasive carcinoma with apocrine differentiation can be associated with germline *PTEN* mutations (Cowden syndrome).

Several other susceptibility genes involved in DNA damage repair are also associated with triple-negative disease, including *BRCA2*, *PALB2*, *RAD51C*, *RAD51D* and *BARD1* variants.[5,154] Analysis of the BRIDGES data set found that germline variants in nine of the breast cancer susceptibility genes (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, *BARD1* and *TP53*) accounted for 27.3% of all triple-negative breast cancers in women aged 40 years or younger.[5] Breast carcinomas with MMR deficiency were significantly more likely to be ER-/PR-negative than MMR-proficient tumours; however, the difference in HER2 expression was not statistically significant.[96]

Hormone receptor-positive

BRCA2-associated breast cancers are more frequently ER-positive and of luminal A or B intrinsic molecular subtype compared to *BRCA1*-associated tumours.[151,155] Indeed, evaluation of the BRIDGES data set found that while *BRCA2* pathogenic variants showed a strong association with the triple-negative phenotype, they were most highly associated with hormone receptor-positive, HER2-negative disease.[5] Furthermore, high-grade ER-positive disease was found to be modestly predictive of *BRCA2* mutation status, irrespective of age.[153] *PALB2* variants are also highly associated with hormone receptor-positive, HER2-negative subtypes in addition to triple-negative disease.[5] *ATM* variants are most commonly associated with ER-/PR-positive, HER2-negative (luminal B) subtype.[5,138,156,157] *CHEK2* variants are associated with all intrinsic breast cancer subtypes except for triple-negative breast cancer.[5,143–146] Of the few reported breast cancer phenotypes in Peutz–Jeghers syndrome, most comprised ER-positive, HER2-negative disease.[158] The polygenic risk score may also inform intrinsic subtype-specific risks corresponding to ER-positive versus ER-negative breast cancers.[9,124,126]

HER2-positive

TP53 pathogenic variants consistently show a strong association with HER2 positive breast cancer.[5,159,160] A study of 24 breast carcinomas arising in the context of neurofibromatosis type 1 demonstrated a higher prevalence of ER-negative, HER2-positive cases compared to age-matched controls, particularly in women aged less than 50 years.[136] It should be noted that while *BRCA1/2*-associated breast carcinomas were more significantly enriched for other subtypes, a lower but increased risk of HER2-positive disease was also identified in mutation carriers, while *CHEK2* variants showed similarly elevated odds ratios for HER2-positive and hormone receptor-positive/HER2-negative disease.[5]

Molecular testing and therapeutic implications

GERMLINE TESTING

Germline testing detects heritable mutations present in the genome and is typically performed on a blood sample. Guidelines from expert groups such as the National Comprehensive Cancer Council (NCCN) outline criteria for germline testing based on factors such as age at breast cancer diagnosis, family history and tumour characteristics.[161] For example, according to current NCCN guidelines, germline testing is recommended for all women diagnosed with triple-negative breast cancer as well as for women with ILC who have a personal or family history of diffuse gastric cancer.[161] In England, the National Genomic Test Directory outlines the eligibility criteria for genetic testing in suspected cases of inherited breast cancer.[162] According to the directory, patients who meet the testing criteria for inherited breast and ovarian cancer are eligible for germline *BRCA1*, *BRCA2*,

PALB2, *ATM* and *CHEK2* testing. In addition, several hereditary breast cancer risk assessment models have been devised, largely aimed at identifying patients with pathogenic variants in *BRCA1/2*,[163–165] although ongoing revisions of some models have allowed for a more broad assessment of genetic risk.[166] Nonetheless, genetic testing guidelines and risk assessment models may miss a significant proportion of patients with clinically actionable germline susceptibility variants,[167–169] and it was found that almost 50% of breast cancer patients with pathogenic or probably pathogenic variants in known susceptibility genes did not qualify for germline testing based on genetic testing guidelines.[167] In view of this, the American Society of Breast Surgeons has recently recommended that germline testing be offered to all breast cancer patients.[170] The increasing availability of NGS, combined with decreased cost and removal of gene patents, has allowed for routine implementation of multigene panel testing among multiple established breast cancer risk genes and the addition of the polygenic risk score, may further refine the accuracy of breast cancer risk stratification in hereditary breast cancer.[171–173] Germline testing results inform screening and risk reducing interventions and have implications for breast cancer management. For example, according to NCCN guidelines, there is currently sufficient evidence to consider risk reducing mastectomy in the setting of germline *BRCA1/2*, *PALB2*, *TP53* and *CDH1* mutations.[161] Furthermore, given that *TP53* mutations are associated with an increased susceptibility to radiation-induced malignancies,[174] identification of germline *TP53* mutations modifies screening and management recommendations in order to minimise radiation exposure in this patient cohort.[55,175]

SOMATIC TESTING

Molecular testing can be performed on the tumour to identify clinically actionable somatic driver mutations, treatment resistance-associated mutations and to assess for gene expression profiles and mutational signatures that have prognostic and therapeutic implications. For example, the commercially available multigene expression assay Oncotype DX evaluates the expression of multiple cancer-related genes to generate a recurrence risk score which is prognostic for recurrence risk and predictive of adjuvant chemotherapy benefit in early-stage ER-positive, HER2-negative breast cancer.[176,177] In the advanced breast cancer setting, somatic testing can be utilised to identify clinically actionable mutations that may inform therapeutic options and clinical trial opportunities. Identification of *PIK3CA* mutations predicts response to adjuvant treatment with alpelisib in hormone receptor-positive, HER2-negative breast cancer, while detection of *ESR1* mutations predicts resistance to hormone therapy.[178] Testing for MMR deficiency, MSI status and/or tumour mutation burden (TMB) may have a role in the advanced disease setting as the US Food and Drug Administration (FDA) has approved immunotherapy with pembrolizumab for patients with unresectable or metastatic solid tumours that are MMR-deficient or TMB-high and have progressed on initial treatment.[179] Immune check-point inhibitors are also FDA-approved for metastatic triple-negative breast cancers that show evidence of programmed death ligand 1 (PD-L1) expression on immunohistochemistry.[178] The predictive value of somatic *BRCA1/2* mutations has not been definitively established in the breast cancer setting.[180]

HOMOLOGOUS RECOMBINATION DEFICIENCY AND PARP INHIBITORS

Poly [adenosine diphosphate (ADP)-ribose] polymerase (PARP) inhibitors, which inhibit the PARP enzymes from repairing single-strand DNA breaks, induce synthetic lethality in the presence of HRD.[181] BRCA1/2 proteins are central to the HR repair pathway and impaired *BRCA1/2* gene function renders tumour cells susceptible to PARP inhibitor therapy.[182–184] Clinically, adjuvant treatment with PARP inhibitors was associated with improved outcomes in patients with *BRCA1/2*-associated breast cancer,[185–189] and hereditary breast cancer management guidelines have incorporated PARP inhibitors in the treatment of advanced *BRCA1/2*-associated breast cancers and, more recently, in the setting of high-risk early-stage HER2-negative disease.[175,190] Germline *BRCA1/2* mutation testing is the recommended method of identifying breast cancer patients who may benefit from PARP inhibitor therapy, as there are currently few data on the clinical outcomes of patients with breast cancers harbouring somatic *BRCA1/2* mutations.[191] However, a significant proportion of breast cancers may be associated with an HRD phenotype independent of *BRCA* germline status as a result of germline mutations in other pathway mediators (e.g. *PALB2*), epigenetic changes (e.g. somatic methylation of *BRCA1* promoter), somatic mutational dysregulation of associated genes or, indeed, occurring through no obvious cause.[192] There is emerging evidence that this expanded patient cohort may also benefit from PARP inhibitor therapy.[193,194] Several testing methods have

been developed to determine HRD status, including germline testing for mutations in HR pathway genes, detection of somatic genomic scars and mutational signatures associated with the HRD phenotype through various tumour-based genomic analyses, as well as functional assessments of HR repair pathway deficiency.[195–198] However, it is not yet clear which of these assays is the most reliable method of determining HRD status or the predictive value of HRD biomarkers in identifying breast cancer patients who may benefit from PARP inhibitor therapy.

Summary

Hereditary breast cancer accounts for a substantial proportion of breast cancer cases. Some of the genetic risk can be explained by pathogenic variants in highly and moderately penetrant breast cancer susceptibility genes, several of which are also associated with recognisable cancer predisposition syndromes. Polygenic risk is also an established contributor to breast cancer risk. Characterisation of the genetic basis of breast cancer is central to the understanding of breast cancer biology and behaviour, which informs genetic testing recommendations and has significant implications for accurate risk prediction, patient management and surveillance.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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