Overview of hereditary breast and ovarian cancer syndromes

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INTRODUCTION

Most women with breast or ovarian cancer have a sporadic rather than an inherited cancer. Although the majority of women with inherited breast and/or ovarian cancers carry a pathogenic variant (ie, deleterious or harmful mutation) in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*), some hereditary breast cancers are due to other rare hereditary syndromes, such as Li-Fraumeni and Cowden syndromes, which are associated with pathogenic variants in the tumor protein p53 and phosphatase and tensin homolog tumor suppressor (*PTEN*) genes, respectively. Pathogenic variants in other genes also confer a heightened risk of breast and/or ovarian cancer.

This topic will present an overview of hereditary breast and ovarian cancer syndromes and risk reduction for breast and gynecologic cancers. However, risk reduction of other cancers associated with pathogenic variants in high-penetrance genes, as well as many of the moderate-penetrance genes, is discussed in other dedicated topics. In such instances, relevant links are provided in the sections below.

Additionally, details regarding who should be offered genetic risk evaluation, how diagnosis of these syndromes should be made, as well as a more focused discussion of the *BRCA1/2*-associated hereditary breast and ovarian cancer syndromes are covered separately.

- (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)
- (See "Cancer risks in BRCA1/2 carriers".)

HIGH-PENETRANCE GENES

Below we cover genes in which pathogenic variants confer high risks of breast and/or ovarian cancer, and other cancers. Specific management guidelines are available to manage patients and are briefly discussed here, with emphasis on management of breast and gynecologic cancers.

BRCA1/BRCA2 — Mutations in either of the breast cancer type 1 or 2 susceptibility genes (*BRCA1/2*) form the majority of hereditary breast and ovarian cancers with an identified pathogenic variant in a cancer susceptibility gene. Overall, pathogenic variants in these genes are implicated in about 15 percent of women with familial breast cancer and a similar proportion of all women with incident ovarian cancers. Cancer risks and management of BRCA1/2 carriers is discussed in detail elsewhere. (See "Cancer risks in BRCA1/2 carriers".)

TP53 (Li-Fraumeni syndrome)

- **Risks** – Li-Fraumeni syndrome (LFS) is associated with germline pathogenic variants in the tumor protein p53 gene (*TP53*), and carriers are at increased risk of developing multiple primary cancers in childhood or young adulthood [1-3]. Overall, women have a lifetime cancer risk approaching 100 percent, although their risk is not exclusively associated with a heightened breast cancer risk. Associated malignancies aside from breast cancer include sarcomas, brain cancer, leukemias, medulloblastoma, and adrenocortical cancers. Although ovarian, fallopian tube, and peritoneal cancers have not been widely reported in families with LFS, *TP53* mutations have been identified in women with these cancers [4], and one large case-control study suggested an association between *TP53* mutations and ovarian cancer [5].

  Women with LFS are at high risk for premenopausal breast cancer versus breast cancer later in life. While the lifetime risk of breast cancer development for female mutation carriers approaches 50 percent by age 60 years, the mean age of onset is under 35 years, and a first diagnosis of breast cancer is rare over age 50 years [2,3,6-10]. Over 50 percent of breast cancers in these carriers are positive for human epidermal growth factor receptor 2 [11]. In addition, carriers are at increased risk of developing secondary malignancies in radiation fields [12]. Therefore, female carriers with breast cancer who

receive radiotherapy are at increased risk for new primaries, especially within the breast, as well as radiation-induced cancers [13].

- **Management** – Women with LFS are typically offered risk-reducing mastectomy (RRM), although some may opt instead for early breast cancer screening supplemented with magnetic resonance imaging (MRI). We offer risk-reducing bilateral salpingo-oophorectomy (rrBSO) to carriers who have a family history of ovarian cancer [14]. Further discussion on the surveillance and management of those with LFS is found elsewhere. (See "Li-Fraumeni syndrome", section on 'Cancer surveillance strategy'.)

  Women with LFS who develop breast cancer are generally recommended to undergo mastectomy, rather than lumpectomy and radiation, given the risks of radiation-induced malignancies in this syndrome [15]. Other clinical manifestations of LFS, and management of other cancer risks, are discussed separately. (See "Li-Fraumeni syndrome", section on 'Management'.)

STK11 (LKB1, Peutz-Jeghers syndrome)

- **Risks** – Peutz-Jeghers syndrome (PJS) is a rare disorder associated with pathogenic variants in the serine/threonine kinase 11 gene (*STK11,* also called *LKB1*) [16]. Mucocutaneous pigmented lesions occur in approximately 95 percent of affected patients; additionally, hamartomatous polyps in the gastrointestinal tract are hallmark features [17]. This syndrome is associated with very elevated risks for gastrointestinal cancers, including cancers of the colon and rectum, stomach, small intestine, and pancreas, as well as breast and ovarian cancers, although ovarian cancers are often sex-cord stromal tumors, which are nonepithelial in origin [17].

  The absolute risk of breast cancer is approximately 32 to 54 percent [14]. In general, the diagnosis tends to occur in younger women, with a mean age of 37 years (range, 9 to 48 years) [17,18].

  For ovarian cancer, the prevalence in one study was 21 percent among patients with PJS, diagnosed at a mean age of 28 years (range, 4 to 57 years) [17]. Further discussion of PJS is covered separately. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

- **Management** – For women with PJS, we initiate early breast cancer screening with supplemental MRI starting at age 30 years. We also offer RRM as an option. Screening for endometrial and ovarian cancer in women with PJS is controversial. Further discussion of

screening for these and other cancers in individuals with PJS is found elsewhere. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

PTEN (PTEN hamartoma tumor syndrome)

- **Risks** – The phosphatase and tensin homolog tumor suppressor gene (*PTEN*) hamartoma tumor syndrome (PHTS) includes Cowden syndrome, which is the predominant disorder. All are associated with germline pathogenic variants in the *PTEN* gene [19]. Carriers have elevated risks for breast, endometrial, and thyroid cancer, particularly follicular cancer [14]. A 2023 report also demonstrated that carriers have an increased risk of colon polyposis and possibly ovarian cancer [20].

  Previous studies of patients with Cowden syndrome reported that the breast cancer risk in women was between 40 to 60 percent [14]. However, in a prospective study of almost 3400 patients meeting relaxed International Cowden Consortium PHTS criteria, including 368 individuals with a pathogenic variant, the estimated lifetime risk of developing breast cancer was 85 percent [21]. Most cancers are diagnosed premenopausally; in one study, 50 percent were diagnosed by age 50 [21].

  It is estimated that up to 67 percent of women with a *PTEN* pathogenic variant also have an increased risk of benign breast changes (eg, intraductal papillomatosis, adenosis, lobular atrophy, and fibroadenomas). However, benign breast findings are not included in the National Comprehensive Cancer Network (NCCN) diagnostic criteria [14].

- **Management** – Women with PHTS are typically offered RRM, although some may opt instead for early breast cancer screening supplemented with MRI. Further discussion is found elsewhere. (See "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Cancer surveillance'.)

  Although pathogenic variants in *PTEN* do not appear to confer a significantly increased risk for ovarian cancer, we discuss the potential risks and benefits of rrBSO with carriers who have a family history of ovarian cancer [14].

  Management of other cancer risks associated with *PTEN* pathogenic variants is discussed elsewhere. (See "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Management'.)

CDH1 (Hereditary diffuse gastric cancer syndrome)

- **Risks** – Hereditary diffuse gastric cancer (HDGC) is characterized by a susceptibility to diffuse, highly invasive gastric cancer (also called signet ring carcinoma or isolated cell-

type carcinoma) [22]. It is associated with germline pathogenic variants in the cadherin 1 gene (*CDH1*) [23,24]. Germline *CDH1* mutations are also associated with development of lobular breast cancer in women, with a cumulative lifetime risk estimated to be as high as 50 to 60 percent [22-26].

CDH1 pathogenic variants can cosegregate with invasive lobular breast cancer in the absence of diffuse gastric cancer, suggesting that gastric cancer is not an obligatory hallmark of families with *CDH1* mutations [27]. Most *CDH1* mutation carriers develop cancer before age 40 [22]. Identification of high-risk families and management of individuals who test positive for *CDH1* are described separately. (See "Hereditary diffuse gastric cancer".)

CDH1 pathogenic variants have been identified in up to 50 percent of affected kindreds who meet the clinical criteria for HDGC. However, with increased testing by multigene panels, several individuals with pathogenic variants in *CDH1* have been identified who do not meet diagnostic testing criteria for HDGC [28].

- **Management** – For those with pathogenic variants in *CDH1,* we typically initiate annual mammography with tomography and annual breast MRI, starting at age 30 years. Use of tomography is preferred in this population to increase cancer detection rates relative to mammography alone. We also offer RRM as an option [14]. (See "Breast imaging for cancer screening: Mammography and ultrasonography", section on 'Digital breast tomosynthesis (DBT)'.)

  Although pathogenic variants in *CDH1* do not appear to confer a significantly increased risk for ovarian cancer, we discuss the potential risks and benefits of rrBSO with carriers who have a family history of ovarian cancer. (See "Hereditary diffuse gastric cancer", section on 'Surveillance for breast cancer'.)

  Management of risks of gastric cancer is discussed elsewhere. (See "Hereditary diffuse gastric cancer", section on 'Management of CDH1 variant carriers'.)

PALB2 — Partner and localizer of *BRCA2* (*PALB2*) is a breast cancer susceptibility gene that encodes a *BRCA2*-interacting protein [29,30] (table 1). The *BRCA2-PALB2* interaction is crucial for key *BRCA2* DNA damage response functions as well as tumor suppression activity [31,32]. (See "Gene test interpretation: *PALB2* (hereditary breast, ovarian, and pancreatic cancer susceptibility gene)".)

- **Risks** – The cumulative lifetime breast cancer risk to age 80 for all female carriers is approximately 53 percent, whereas the cumulative risk to age 50 is approximately 17

percent [33]. In two large cohort studies, there was a greater association for estrogen receptor (ER)-negative breast cancer than for ER-positive breast cancer among *PALB2* carriers [34,35]; for example, in one study, the odds ratios relative to noncarriers were 9.2 for ER-negative cancers and 3.1 for ER-positive cancers [35].

In comparison with the general population, the relative risk of breast cancer for a woman with a *PALB2* pathogenic variant based upon her age is [36]:

- Under 40 years – Eight- to ninefold increase
- 40 to 60 years – Six- to eightfold increase
- Over 60 years – Fivefold increase

Given this range of risk, and that the upper risk range can overlap with *BRCA2* risks, *PALB2* is considered to be a moderate- to high-risk gene associated with hereditary breast cancer [36-39]. Breast cancer risk associated with a *PALB2* pathogenic variant appears to be influenced by birth cohort, a family history of breast cancer, and other as yet unidentified environmental and lifestyle factors [33,36]. In an international study of 524 families with a *PALB2* pathogenic variant, the absolute lifetime risk to age 70 years for the development of female breast cancer was dependent upon family history of breast cancer, as follows [36]:

- No family history of breast cancer – 33 percent
- Two or more family members with breast cancer – 58 percent

Although rare, monoallelic deleterious *PALB2* pathogenic variants are present in a small but substantial proportion of patients with breast cancer [36,40], including approximately 1 percent of patients with breast cancer and approximately 1 percent of patients with triple-negative breast cancer [41,42]. In high-risk families, pathogenic *PALB2* variants were identified in 3.9 percent (13 of 409) of breast and/or ovarian cancer patients in the Czech Republic who were negative f*or BRCA1/2* mutations [43]. Prospective data from one study indicate that among premenopausal *PALB2* carriers with ER-negative breast cancer, the 10-year cumulative risk of contralateral breast cancer is 35 percent [44].

Several studies have shown that *PALB2* pathogenic variants are associated with a low absolute risk of ovarian cancer (on the order of 3 to 5 percent) [4,14,33,45]. Pathogenic variants are also associated with an increased risk of pancreatic cancer (2 to 3 percent), although the absolute risk is unclear [33,46,47]. In addition, there may also be an association with increased risks for breast cancer in men (1 percent), prostate cancer, and medulloblastoma, although these risks are not confirmed and are difficult to quantify [4,33,48-51].

Biallelic mutations in the *PALB2* gene, also known as *FANCN*, cause Fanconi anemia [52]. (See "Clinical manifestations and diagnosis of Fanconi anemia", section on 'Genetics'.)

- **Management** – For women with pathogenic variants in *PALB2*, we initiate annual mammography with tomography and annual breast MRI, starting at age 30 years. We also offer RRM as an option [14]. There are no data about efficacy of hormonal chemoprevention (tamoxifen or aromatase inhibitor); moreover, studies have found that there is an increased risk of triple-negative breast cancer in *PALB2* carriers. Therefore, the benefits of this approach are unknown in *PALB2* carriers.

  Additionally, we suggest rrBSO for carriers >45 years [14].

  Screening for pancreatic cancer in *PALB2* carriers with relevant family history is discussed elsewhere. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Candidates for screening' and "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Screening modality and timing'.)

MSH1, MLH1, MSH6, PMS2, and EPCAM (Lynch syndrome)

- **Risks** – Lynch syndrome, also called hereditary nonpolyposis colon cancer, is associated with pathogenic variants in mismatch repair (MMR) genes (*MSH2, MLH1, MSH6, and PMS2*) and pathogenic variants in the epithelial cell adhesion molecule gene (*EPCAM*) [5,53,54]. The cumulative lifetime risks for the major cancers associated with the various genetic alterations associated with Lynch syndrome are as follows [14,55]:

  - Colon –
    - *MLH1*: 46 to 61 percent.
    - *MSH2* and *EPCAM*: 33 to 52 percent.
    - *MSH6*: 10 to 44 percent.

  - Endometrium –
    - *MLH1*: 34 to 54 percent.
    - *MSH2* and *EPCAM*: 21 to 57 percent.
    - *MSH6*: 16 to 49 percent.

  - Ovaries –
    - *MLH1*: 4 to 20 percent.
    - *MSH2* and *EPCAM*: 8 to 38 percent. *MSH2* has been implicated as a genetic cause of very young ovarian cancer, with the likelihood of an epithelial ovarian cancer in

MSH2 heterozygotes being >2 percent by age 35 (compared with less than 0.5 percent for *BRCA1/2*) [56].

- *MSH6*: <1 to 13 percent.

- Stomach –
  - *MLH1*: 5 to 7 percent.
  - *MSH2* and *EPCAM*: 0.2 to 9 percent.
  - *MSH6*: <1 to 8 percent.

Some, but not all, studies have suggested that there is an increased risk of female breast cancer in mutation carriers of MMR genes [53,57,58]. In a review of 21 studies, 13 found no statistical increase in breast cancer risk, and 8 reported an increased risk ranging from 2- to 18-fold compared with the general population [59]. Two large subsequent cohort studies have found no statistically significant risk of breast cancer with the MMR genes [34,35]. Given the inconsistency in data about breast cancer risk in Lynch syndrome, further data are required.

Multigene panel testing is identifying individuals with pathogenic variants in Lynch syndrome genes who do not meet diagnostic criteria for Lynch syndrome. For example, in a study of 528 patients with Lynch syndrome pathogenic variants identified by multigene panel testing, about 73 percent met NCCN guidelines for Lynch syndrome, only 22 percent met NCCN testing criteria for *BRCA1/2* and not Lynch syndrome criteria, and 5 percent met neither *BRCA1/2* nor Lynch syndrome testing criteria [60]. Among patients who met *BRCA1/2* testing criteria, pathogenic variants in *MSH6* and *PMS2* were more common than the other MMR genes.

- **Management** – rrBSO and hysterectomy for ovarian and endometrial cancer risk reduction is typically suggested for women with Lynch syndrome, upon completion of childbearing. Breast cancer risk is managed based on the patient's risk level based on other factors, including family history, and may include early breast cancer screening, possibly with MRI [14,61-63]. Further discussion of Lynch syndrome is covered separately. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer", section on 'Candidates' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management".)

Screening for other cancers in patients with Lynch syndrome (eg, pancreatic, in those with a family history) is discussed elsewhere. (See "Lynch syndrome (hereditary nonpolyposis

colorectal cancer): Cancer screening and management", section on 'Screening for Lynch-associated cancers'.)

MODERATE-PENETRANCE GENES

General considerations — In addition to well-described familial syndromes and high-penetrance gene variants associated with an increased risk of breast and/or ovarian cancer, pathogenic variants in other genes at least moderately increase the risk of these cancers [34,35]. Some classification systems also include partner and localizer of *BRCA2* (*PALB2)* as a moderate-penetrance gene. (See 'PALB2' above.)

- **Risks** – Women who have pathogenic variants in neurofibromatosis type 1 (*NF1*), ataxia-telangiectasia mutated (*ATM*), checkpoint kinase 2 (*CHEK2*), or breast cancer susceptibility gene 1 (*BRCA1)*-associated RING domain 1 (*BARD1*) have a moderate lifetime risk of breast cancer, and those with mutations in RAD51 paralog C (*RAD51C*) or RAD51 paralog D (*RAD51D*) have a moderate lifetime risk for breast or ovarian cancer, and as such are managed with surveillance and risk reduction strategies. Estimated average five-year and cumulative breast cancer risks for women with pathogenic variants in moderate to high penetrance are useful for counseling purposes (table 1) [34,35,39].

  Several large case-control studies have described the associations between a number of possible cancer susceptibility genes and the risk of breast cancer [5,41]. As examples:

  - Two large case-control studies have described the associations between a number of possible cancer susceptibility genes and the risk of breast cancer. The international study included 113,000 women from 25 countries, and evaluated 34 genes [34]; separately, 28 genes were evaluated in 64,000 women from the United States [35]. Aside from *BRCA1* and breast cancer susceptibility gene 2 (*BRCA2)*, variants in *PALB2*, *BARD1*, *RAD51C*, *RAD51D*, *ATM*, and *CHEK2* were associated with breast cancer risk in both studies. Lifetime risks of several commonly mutated genes are shown in the figure (figure 1).

  - These studies also quantified the risk of estrogen receptor (ER)-positive and ER-negative breast cancers (table 2 and figure 2).

  Given the size and design of these studies, these studies provide the most comprehensive assessment of risk to date.

Cancer risks for pathogenic variants in other genes are less well established. Commercial multigene panels include testing for the *BRCA1/2* genes, the high-risk genes listed above, as well as several moderate-risk genes and newer genes with preliminary evidence for associations with heightened cancer risks.

Patients who test positive for a pathogenic variant or a variant of uncertain significance in these and other rare genes may participate in an online registry called Prospective Registry of Multiplex Testing, a collaborative effort among academic institutions and commercial labs in the United States to learn more about how to interpret these results [64].

- **Considerations regarding surveillance and risk management** – Decisions about chemoprevention and risk-reducing mastectomy (RRM) and/or salpingo-oophorectomy should be highly individualized based upon the woman's mutation status as well as personal and family history. Individualized recommendations should also take into account the patient's personal risk factors and family history, which may affect the age that screening modalities start (eg, 5 to 10 years before the earliest age of breast cancer diagnosis in the family), whether MRI is recommended, and whether mastectomy is offered. For women with pathogenic variants in other genes that are not known to be associated with increased risks for breast cancer, if models estimate their lifetime risk of breast cancer is 20 percent or higher, MRI screening is recommended [65]. Some such women may also be candidates for chemoprevention against breast cancer, depending on their personal and family history. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

  With respect to ovarian cancer screening in women with pathogenic variants in the moderate-penetrance genes, we typically do not recommend either imaging or cancer antigen 125 measurements given the limited efficacy; however, we may recommend risk-reducing bilateral salpingo-oophorectomy (rrBSO) for some patients based on their genetic testing results, such as for *RAD51C* carriers. (See 'RAD51 paralogs' below.)

CHEK2 — The checkpoint kinase 2 (*CHEK2*) gene is associated with the DNA damage repair response Fanconi anemia (FA)-*BRCA1/2* pathway [66,67]. (See "Gene test interpretation: *CHEK2*".)

- **Risks** – Studies have found that *CHEK2* carriers have increased risks for breast cancer (particularly ER-positive breast cancers), male breast cancer, stomach, prostate, kidney, leukemia, plasma cell neoplasms, thyroid cancer, and sarcoma [68-70]. Although some studies found that specific *CHEK2* variants have been associated with an increased lifetime risks of colorectal cancer (11 percent in 1100delC carriers; 9 percent in I157T carriers) [71],

a recent large study of 3783 *CHEK2* carriers, including those with 1100delC and I157T, found no increased risk [72]. There is no strong evidence that *CHEK2* mutations confer an increased risk of ovarian cancer given how infrequently they are identified in women with ovarian cancer [4,73].

It is critical to review the genetic testing report carefully (algorithm 1). Risk information and associated management recommendations for variants in the *CHEK2* gene may be dependent on the specific variant identified.

Several *CHEK2* variants have been identified [72,74], including one polymorphism (1100delC) that appears to be associated with a low- to moderate-penetrance breast cancer susceptibility allele [68,72,74-80].

- **1100delC protein-truncating variant** – The 1100delC protein-truncating variant is associated with a two- to threefold increased risk of breast cancer, particularly hormone receptor-positive cancer, and occurring predominantly among White Americans and Europeans of Northern or Eastern European descent [68,81-86]. The cumulative risk of breast cancer has been estimated to be 37 percent by age 70 years [87] and 32 percent by age 80 in another study [39]. The latter study, estimated a 6 percent cumulative risk to age 49.

  There are several significant differences between mutation carriers and noncarriers with breast cancer. For example, in one study, compared with noncarriers, *CHEK2* carriers of the 100delC variant were significantly more likely to [83]:

  - Be younger at the time of diagnosis (mean age, 50 versus 54)
  - Have a family history of breast cancer (13 versus 10 percent)
  - Develop ER-positive breast cancers (63 versus 57 percent)
  - Develop a second primary breast cancer (hazard ratio [HR] 3.52, 95% CI 2.35-5.27)

- **Other variants** – A large retrospective cohort study of 3783 participants found that certain missense variants in *CHEK2* (I157T, S428F, and T476M), which occurred in 42 percent of the sample, were associated with a lower risk of breast cancer than the 1100delC protein-truncating variant and were not associated with risks for other types of cancer [72]. Similarly, a meta-analysis of 18 case-control studies found that the I157T variant is associated with only a modest increase in breast cancer risk (odds ratio [OR] 1.58, 95% CI 1.42-1.75) [88]. Estimated age-specific risks for the I157T variant indicate that the cumulative lifetime risk of breast cancer to age 80 is approximately 18 percent, whereas the cumulative risk of breast cancer to age 49 is approximately 3 percent [39].

Family history of breast cancer has been shown to impact breast cancer risk in *CHEK2* carriers [86]. An international study of over 26,000 breast cancer cases and 26,000 controls suggested that polygenic risk score modulated breast cancer risk. By age 80, *CHEK2* carriers with no family history of breast cancer had a 15 percent likelihood of breast cancer if they were in the 10^{th} percentile for polygenic risk scores (PRS), whereas their risk was 37 percent if they were in the 90^{th} percentile for PRS [89].

Prospective data from one study show that among premenopausal *CHEK2* carriers the 10-year cumulative risk of contralateral breast cancer is 13 percent, and 4 percent for postmenopausal patients [44].

- **Management** – For those with pathogenic variants in *CHEK2,* we typically initiate annual mammography with tomography at age 40 years and offer annual MRI, starting at age 30 to 35 years, given evidence of moderately increased lifetime risk of breast cancer. There is insufficient risk to support a recommendation for RRM, although for those with a concerning family history or other risk factors (eg, atypia or a breast cancer diagnosis), it may be reasonable to consider this option [14,90].

  For select women at risk for breast cancer, chemoprevention with endocrine therapy may be an appropriate option, particularly as women with *CHEK2* mutations are more likely to develop ER-positive breast cancers [91]. However, no data are available regarding efficacy specifically in this group of mutation carriers. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

  Pathogenic variants in *CHEK2* do not appear to confer a significantly increased risk for ovarian cancer. For carriers who have a family history of ovarian cancer, we discuss the potential risks and benefits of rrBSO. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer".)

  Although data about the risk of colorectal cancer are conflicting, we agree with National Comprehensive Cancer Network (NCCN) recommendations for carriers without a first-degree relative with colorectal cancer to undergo colonoscopy every five years, beginning at age 40. For those with a first-degree relative with colorectal cancer, colonoscopy should be performed every five years beginning either at age 40, or 10 years prior to the age of the first-degree relative's age at colorectal cancer diagnosis [92].

  Shared decision making between male *CHEK2* carriers and their clinicians regarding prostate cancer screening should begin at age 40 years.

ATM — Heterozygotes for a single pathogenic AT are at increased risk for some cancers (algorithm 2). (See "Gene test interpretation: *ATM* (ataxia-telangiectasia, breast cancer, and pancreatic cancer susceptibility gene)".)

- **Risks** – Monoallelic carriers of such pathogenic variants (ie, heterozygotes) are at approximately twofold higher risk of developing breast cancer than noncarriers, with a cumulative lifetime breast cancer risk of approximately 20 to 40 percent (and 6 percent to age 49) [14,39,93-97]. In two large cohort studies, there was a greater association for ER-positive breast cancer than for ER-negative breast cancer, among ataxia-telangiectasia mutated (*ATM*) carriers [34,35]; for example, the OR was approximately 2.0 to 2.3 for ER-positive disease in carriers relative to the noncarriers (versus approximately 1.0 for ER-negative disease). Rare pathogenic variants in the *ATM* gene may be associated with a substantially higher risk of breast cancer, so risk assessment based on genotype can be important [94,95]. The risk of second primary breast cancer is not clear [98]. Although it is also possible that there is an increased risk of ovarian cancer based on results of a case-control study [5], these data need to be confirmed.

  It is estimated that approximately 3 percent of White people in the United States are *ATM* heterozygotes [99]. In a retrospective study of 443 *BRCA1/2*-negative familial breast cancer patients and 521 control breast cancer patients, *ATM* mutations were more commonly identified in patients with familial breast cancer compared with the control population (12 versus 2 deleterious *ATM* mutations) [93]. Relatives of individuals with AT, especially obligate carrier mothers of affected children, should be informed about the elevated cancer risks and potential screening strategies.

  ATM pathogenic variants have also been associated with increased risks for pancreatic cancer [70,100], with an absolute risk estimated at 5 to 10 percent [14]. There may also be somewhat higher risks of ovarian cancer, prostate cancer, and gastric cancer, but more data are needed to confirm these findings [5,70]. The potential increased risk for this and other cancers has not been well characterized. (See "Gene test interpretation: *ATM* (ataxia-telangiectasia, breast cancer, and pancreatic cancer susceptibility gene)".)

  In regards to noncancer risks, heterozygotes for a single pathogenic AT variant are also at possibly higher risk of coronary artery disease [101].

  Pathogenic biallelic variants in the *ATM* gene give rise to AT. AT is discussed in more detail separately. (See "Ataxia-telangiectasia".)

- **Management** – For those with pathogenic variants in *ATM,* we typically initiate annual mammography with tomography at age 40 years, and offer annual MRI, starting at age 30

to 35 years, given evidence of moderately increased lifetime risk of breast cancer [14]. In light of the higher risk of breast cancer associated with the c.7271T>G variant, surveillance may begin at age 25 with breast MRI and the addition of annual mammography beginning at age 30 [101]. There is insufficient risk to support a recommendation for RRM, although for those with a concerning family history or other risk factors (eg, atypia or a diagnosis of breast cancer), it may be reasonable for carriers to consider this option [14]. Breast surveillance recommendations may be modified based on genotype and family history [101].

Pathogenic variants in *ATM* do not appear to confer a significantly increased risk for ovarian cancer. For carriers who have a family history of ovarian cancer, we discuss the potential risks and benefits of rrBSO. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer".)

For *ATM* carriers with a family history of pancreatic cancer, pancreatic cancer screening is offered. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Candidates for screening' and "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Screening modality and timing'.)

- **Considerations for *ATM* carriers with cancer –** We generally do not alter our approach to radiation therapy or chemotherapy in individuals who are *ATM* heterozygotes and warrant such treatments. While patients with AT are particularly sensitive to ionizing radiation and chemotherapeutic agents that cause double-stranded breaks in DNA, *ATM* heterozygotes are less sensitive [102]. Preliminary evidence from one observational study of 91 *ATM* mutation carriers receiving radiation for breast cancer did not suggest high rates of toxicity, irrespective of whether the mutations were pathogenic or variants of unknown significance [103]. The clinical impact of such issues is not well known, and, in general, we treat *ATM* heterozygotes with cancer with the "best" standard therapies for their particular cancer, and do not withhold radiation, when indicated [15,101].

  Of note, in one prospective study, the risk of contralateral breast cancer was not elevated in heterozygous *ATM* carriers [44].

BARD1 — *BRCA1*-associated RING domain 1 (*BARD1*) is involved in the FA-*BRCA1/2* pathway. (See 'CHEK2' above.)

- **Risks** – *BARD1* mutations may be cancer-risk alleles and predispose to an increased risk of breast cancer in women, and possibly ovarian cancer as well [4,104,105], on the order of 20 to 40 percent [14]. In two large cohort studies, there was a greater association for ER-negative breast cancer than for ER-positive breast cancer among *BARD1* carriers [34,35];

for example, in one study, the ORs relative to noncarriers were 2.5 for ER-negative cancers and 0.9 for ER-positive cancers [35].

- **Management** – For those with pathogenic variants in *BARD1*, we initiate annual mammograms at age 40, along with consideration of breast MRI with contrast [14]. There is insufficient risk to support a recommendation for RRM, although for those with a concerning family history or other risk factors (eg, atypia or a diagnosis of breast cancer), it may be reasonable for carriers to consider this option. (See "Screening for breast cancer: Strategies and recommendations", section on 'Breast cancer risk determination'.)

RAD51 paralogs — Related genes in the same family are called paralogs, and the *RAD51* paralogs, RAD51 paralog C (*RAD51C*) and RAD51 paralog D (*RAD51D*), are involved in the FA-*BRCA1/2* pathway. Therefore, carriers should be aware of reproductive implications if their partner is also found to have a similar pathogenic variant.

- **Risks** – *RAD51C* and *RAD51D* mutations are rare and confer an increased risk of ovarian cancer (10 to 20 percent), as well as an increase in breast cancer, especially for triple-negative breast cancers [14,34,35,106-114]. The absolute risk of breast cancer is estimated to be between 20 to 40 percent [14].

  - **Breast cancer risks** – In two large cohort studies, there was a greater association for ER-negative breast cancer than for ER-positive breast cancer among carriers of pathogenic variants in *RAD51* paralogs [34,35]; for example, in one study, the ORs relative to noncarriers were 9.2 for ER-negative cancers and 3.1 for ER-positive cancers [35].

  - **Ovarian cancer risks** – *RAD51C* mutations may occur in 1 percent of unselected women with ovarian cancer and are associated with an ovarian cancer risk of approximately 9 to 11 percent [112,114].

    In a case-control study of 3400 women with epithelial ovarian cancer and 2700 controls, both *RAD51* paralogs were associated with a risk of ovarian cancer (*RAD51C* OR 5.2; *RAD51D* OR 12.0) [107]. The estimated cumulative ovarian cancer risk for *RAD51C* carriers is approximately 1 percent by age 49, and the risk to age 80 is approximately 6 percent [39]. In *RAD51D* carriers, the estimated cumulative risk of ovarian cancer is approximately 1 percent by age 49 and is approximately 14 percent to age 80 [39].

- **Management** – For those with pathogenic variants in *RAD51* paralogs, we initiate annual mammogram and offer breast MRI starting at age 40 years. The evidence is insufficient to uniformly recommend RRM, although for those with a concerning family history or other

risk factors (eg, atypia or a diagnosis of breast cancer), it may be reasonable for carriers to consider this option.

rrBSO is recommended between age 45 to 50 years, or earlier if there is a family history of ovarian cancer, particularly if the age of onset was early [14]. We inform women that, although there are no data in these gene carriers, use of oral contraceptives may reduce the risk of ovarian cancer, as observed in women with pathogenic variants in *BRCA1/2* [115].

NF1 — Pathogenic variants in neurofibromatosis type 1 (*NF1*) give rise to neurofibromatosis 1 [116,117], an autosomal dominant syndrome in which affected individuals develop café-au-lait macules, axillary and/or inguinal freckling, peripheral neurofibromas, optic pathway gliomas, soft tissue gliomas, and sarcomas. *NF1* encodes for neurofibromin. Neurofibromin is a member of a family of proteins that affect a number of signaling pathways stimulating cell survival and proliferation [118-120]. (See "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis".)

Women with *NF1* have an increased risk of early-onset breast cancer (generally between age 30 to 40), and do not appear to have an increased risk after age 50 [121,122]. These cancers tend to be associated with poorer survival than the general population [121,122].

Although the lifetime risk of cancer in people with *NF1* is about 60 percent [121], the lifetime breast cancer risk in women is estimated to be between 20 to 40 percent [14].

Females with *NF1* are recommended to begin annual mammography at age 30, and from age 30 to 50 years, consider breast MRI with contrast [14].

Because of the phenotypic associations with *NF1*, most affected individuals have previously received a clinical diagnosis. They are usually followed by a clinical geneticist. If multigene panel testing incidentally identifies an *NF1* carrier who has not had a clinical diagnosis, we would make such a referral and coordinate their care for cancer risk management as needed. (See "Neurofibromatosis type 1 (NF1): Management and prognosis".)

BRIP1 — BRCA-interacting protein 1 (*BRIP1*) is a DNA repair gene that interacts with *BRCA1*. Biallelic germline mutations of this gene result in Fanconi anemia complementation groups [123].

- **Risks** – *BRIP1*-inactivating truncating mutations are hypothesized in several but not all studies to be associated with a slightly increased risk of breast cancer, and have more consistently been linked with a moderately increased risk of ovarian cancer [124-129]. For

example, in a case-control study of 3200 women with ovarian cancer, 3400 healthy controls, and 2000 unaffected women at high risk for ovarian cancer, *BRIP1* was associated with an increased risk of ovarian cancer (relative risk [RR] 11.2) [128]. The cumulative lifetime risk of ovarian cancer to age 80 ranges between approximately 5 and 15 percent depending on the study methodology [39].

- **Management** – For those with pathogenic variants in *BRIP1*, we suggest rrBSO at age 45 to 50 years, per NCCN guidelines [14]. We inform women that, although there are no data in these gene carriers, use of oral contraceptives may reduce the risk of ovarian cancer, as observed in women with pathogenic variants in *BRCA1/2* [115].

  Given that breast cancer risks are not well defined, no guidelines exist about how to manage breast cancer risks in women with pathogenic variants in newly identified genes, including *BRIP1.* In such cases, breast cancer risk may still be assessed based on personal and family history. Such women may wish to discuss the option of RRM, particularly if they have a strong family history.

GENES PREVIOUSLY THOUGHT TO BE IMPLICATED IN BREAST CANCER

BRIP1 — BRCA-interacting protein 1 (*BRIP1*)-inactivating truncating mutations were previously thought to increase risk of breast cancer [130], but more recent and definitive large case-control studies found no increased risk for breast cancer [34,35,131]. There appears to be a stronger link to ovarian cancer. (See 'BRIP1' above.)

MUTYH — mutY DNA glycosylase (*MUTYH*) is a DNA base repair gene that corrects oxidative DNA damage, a critical function to maintain genomic stability and modulate carcinogenesis [132]. While some prior studies have suggested that *MUTYH* heterozygotes have an increased risk of breast cancer [133-135], more recent and definitive large case-control studies found no increased risk for breast cancer [34,35,131], although one has suggested an increased risk of kidney cancer [70]. We do not perform early mammography or breast MRI, unless their family history places them at increased risk.

Homozygous and biallelic carriers have an increased risk of colorectal polyposis and cancer [136-139]. (See "*MUTYH*-associated polyposis", section on 'Colorectal cancer surveillance'.)

NBN — *NBN* encodes the protein nibrin, which is involved with repair of DNA breaks, telomere maintenance, and base excision repair [140-147]. The most common pathogenic variant in patients of Eastern European descent is hypomorphic, leading to a partially functional protein [148]. Other mutations are more common in different populations [149]. Nijmegen breakage

syndrome is an autosomal-recessive disorder caused by pathogenic variants in nibrin and is discussed elsewhere. (See "Nijmegen breakage syndrome".)

While some prior studies have suggested that *NBN* variant carriers have an increased risk of breast cancer [150,151], the more recent and definitive large population-based case-control studies found no increased risk for breast cancer [34,35]. Other studies also failed to demonstrate an association between pathogenic variants in *NBN* and breast cancer [41,152]. We do not perform early mammography or breast MRI, unless their family history places them at increased risk. (See 'Moderate-penetrance genes' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary breast and ovarian cancer" and "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Genetic testing for breast, ovarian, prostate, and pancreatic cancer (The Basics)" and "Patient education: Genetic testing (The Basics)")
- Beyond the Basics topics (see "Patient education: Genetic testing for hereditary breast, ovarian, prostate, and pancreatic cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Introduction** – The majority of women who test positive for a gene associated with hereditary breast and/or ovarian cancers carry a pathogenic breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*). However, pathogenic variants in certain other genes also confer a heightened risk of breast and/or ovarian cancer. (See 'Introduction' above.)

- **High-penetrance genes** – Many of these high-risk syndromes have characteristic presentations, although more widespread use of multigene panel testing has shown that there can be significant variability, and not all individuals who test positive meet established diagnostic criteria for these other syndromes. (See 'High-penetrance genes' above.)

  - **Select cancer syndromes** – Cancer risk management in patients with *BRCA1/2* alterations, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, phosphatase and tensin homolog tumor suppressor (*PTEN*) hamartoma tumor syndrome, hereditary diffuse gastric cancer, and Lynch syndrome are discussed elsewhere. Risk reduction strategies and/or early breast cancer screening and supplemental screening with breast MRI is appropriate in some of these syndromes. (See "Cancer risks in BRCA1/2 carriers" and "Li-Fraumeni syndrome", section on 'Cancer surveillance strategy' and "Li-Fraumeni syndrome", section on 'Cancer management' and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Cancer surveillance' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management", section on 'Candidates for screening' and "Hereditary diffuse gastric cancer", section on 'Surveillance for breast cancer'.)

  - **CDH1** – For women with pathogenic variants in cadherin 1 gene (*CDH1*), we initiate annual mammography with tomography and offer annual bilateral breast MRI starting at age 30 years. We also offer risk-reducing mastectomy (RRM). (See 'CDH1 (Hereditary diffuse gastric cancer syndrome)' above.)

  - **PALB2** – For women with pathogenic variants in partner and localizer of *BRCA2* (*PALB2)*, we initiate annual mammography with tomography and annual bilateral breast MRI starting at age 30 years. We also offer RRM. Pathogenic variants in *PALB2* are associated with a heightened risk for estrogen receptor (ER)-negative breast cancers.

For *PALB2* carriers >45 years, we suggest risk-reducing bilateral salpingo-oophorectomy (rrBSO) (**Grade 2B**), given a small absolute increased risk in ovarian cancer. (See 'PALB2' above.)

- **Moderate-penetrance genes** – Pathogenic variants in less well-characterized genes also contribute to increased risks for breast, ovarian, and other cancers. These genes are included on extended multigene panels. (See 'Moderate-penetrance genes' above.)

  - Women who have pathogenic variants in the genes checkpoint kinase 2 (*CHEK2*) and ataxia-telangiectasia mutated (*ATM*) have a moderate to high lifetime risk of breast cancer, particularly ER-positive breast cancers, while *BRCA1*-associated RING domain 1 (*BARD1*) *and the RAD51* paralogs confer a heightened risk of breast cancers that are more commonly ER-negative.

    - **Screening** – For those with pathogenic variants in *ATM or CHEK2*, we initiate annual mammography with tomography at age 40 years and offer annual breast MRI starting at age 30 to 35 years.

    - For those with pathogenic variants in *RAD51* paralogs (*RAD51C* and *RAD51D*) or *BARD1*, we initiate annual mammogram and offer breast MRI starting at age 40 years.

    - **Breast cancer risk reduction** – *ATM, CHEK2,* neurofibromatosis type 1 (*NF1*), *RAD51C* and *RAD51D* carriers are not felt to be at sufficient risk to recommend RRM, although individual women may also consider it based on their personal and family history.

    - **Ovarian cancer risk reduction** – For those with pathogenic variants in BRCA-interacting protein 1 (*BRIP1*), *RAD51C*, or *RAD51D* we suggest rrBSO beginning when the patient is 45 to 50 years, given evidence for increased ovarian cancer risks (**Grade 2B**). (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer".)

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Topic 785 Version 74.0

GRAPHICS

Estimated average five-year and lifetime breast-cancer risks for women with moderate-penetrance mutations in selected genes

Age (years)	Population		*ATM/NBN* (RR 2.7 to 2.8)*		*CHEK2*(1100delC) (RR 3.0)¶		*CHEK2*(I157T) (RR 1.58)	
	5-year (%)	Cumulative (%)	5-year (%)	Cumulative (%)	5-year (%)	Cumulative (%)	5-year (%)	Cumulativ (%)
25 to 29	0.04	0.1	0.12	0.1	0.13	0.2	0.07	0.1
30 to 34	0.14	0.2	0.38	0.5	0.41	0.6	0.21	0.3
35 to 39	0.30	0.5	0.84	1.4	0.90	1.5	0.48	0.8
40 to 44	0.61	1.1	1.70Δ	3.0	1.83Δ	3.2	0.96Δ	1.7
45 to 49	0.94Δ	2.0	2.64◇	5.6	2.83◇	5.9	1.49Δ	3.2
50 to 54	1.12Δ	3.1	3.14◇	8.5	3.36◇	9.1	1.77Δ	4.9
55 to 59	1.33Δ	4.4	3.71◇	11.8	3.98◇	12.6	2.09Δ	6.8
60 to 64	1.72Δ	6.0	4.81◇	16.0	5.15◇	17.0	2.71◇	9.3
65 to 69	2.11Δ	8.0	5.92◇	20.8	6.34◇	22.1	3.34◇	12.3
70 to 75	2.20◇	10.0	6.17◇	25.5	6.61◇	27.1	3.48◇	15.3
CLTR (80)	**NA**	**12.0**	**NA**	**30.0**	**NA**	**31.8**	**NA**	**18.3**

These data represent the estimated cumulative five-year incidence of breast cancer associated with moderate-penetrance mutations with established clinical validity (based on the method of Song et al[2]).

RR: relative risk; CLTR: cumulative lifetime risk; NA: not applicable.

* *ATM* CLTR (80 years) estimated to be 27.1% with an RR of 5.0 up to age 50 years and then 2.0 thereafter (based on data from Thompson et al[3]). Data for *NBN* derived from study of a single truncating mutation.

¶ *CHEK2* truncating mutation CLTR (80 years) estimated to be 23.4% if RR declines with age (according to the *CHEK2* Breast Cancer Case-Control Consortium[4]).

Δ Indicates the age ranges at which five-year risk approaches or exceeds 1% (the approximate population risk of breast cancer among United States women aged 45 years).

◇ Indicates the age ranges at which the five-year risk of breast cancer exceeds 2.2% (the highest risk estimated for United States women in the general population, specifically, those aged between 70 to 79 years).

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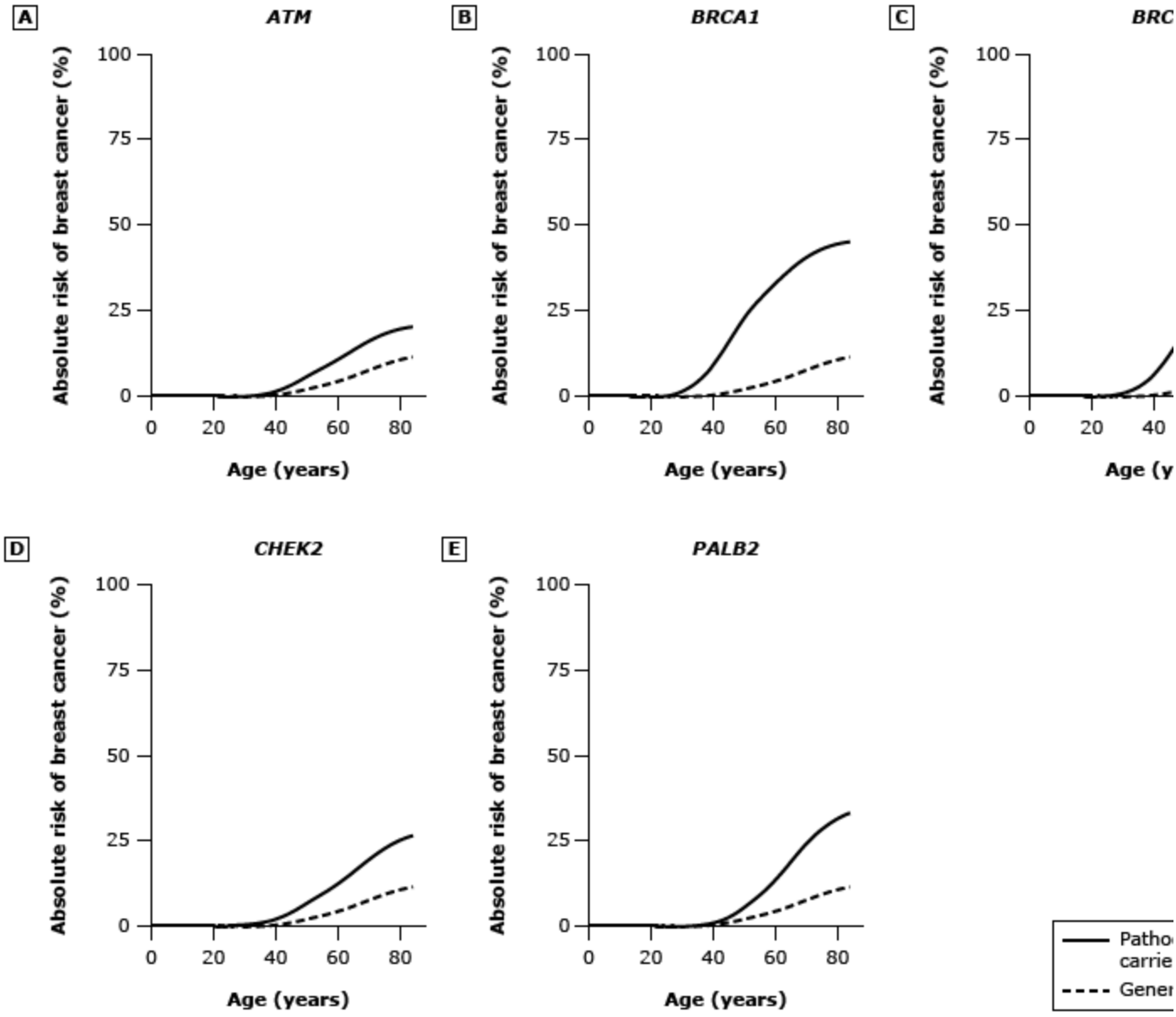
4. *CHEK2 Breast Cancer Case-Control Consortium. CHEK2*1100delC and susceptibility to breast cancer: A collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am J Hum Genet 2004; 74:1175.*

Graphic 118684 Version 8.0

Population-based lifetime absolute risk of breast cancer development according to age and the commonly mutated genes *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*



The CARRIERS consortium studies that were included in the analysis of the absolute risk of breast cancer among pathogenic-variant carriers were the Cancer Prevention Study II, the Cancer Prevention Study 3, the California Teachers' Study, the Mayo Clinic Breast Cancer Study, the Multiethnic Cohort Study, the Mayo Mammography Health Study, the Nurses' Health Study, the Nurses' Health Study II, the Women's Circle of Health Study, the Women's Health Initiative, and the Wisconsin Women's Health Study. The analysis in the general population was performed with the use of age-specific breast cancer incidence data (restricted to non-Hispanic White individuals) from the Surveillance, Epidemiology, and End Results 21 registries.

ATM: ataxia-telangiectasia mutated; *BRCA1*: breast cancer susceptibility gene 1; *BRCA2*: breast cancer susceptibility gene 2; *CHEK2*: checkpoint kinase 2; *PALB2*: partner and localizer of *BRCA2*; CARRIERS: Cancer Risk Estimates Related to Susceptibility Consortium.

Graphic 130571 Version 3.0

Associations between pathogenic variants in established breast cancer: Predisposition genes and risk of breast cancer according to estrogen-receptor and triple-negative breast cancer status of tumors*

Breast cancer-predisposition gene	ER-positive breast cancer (n = 18,428)		ER-negative breast cancer (n = 3805)		Triple-negative breas cancer (n = 1463)	
	Participants with pathogenic variant (Number [%])	Odds ratio (95% CI)¶	Participants with pathogenic variant (Number [%])	Odds ratio (95% CI)¶	Participants with pathogenic variant (Number [%])	Odds ratio (95% CI)¶
ATM	151 (0.82)	1.96 (1.52-2.53)	19 (0.50)	1.04 (0.59-1.72)	5 (0.34)	0.50 (0.12 1.36)
BARD1	20 (0.11)	0.91 (0.49-1.64)	11 (0.29)	2.52 (1.18-5.00)	6 (0.41)	3.18 (1.16 7.42)
BRCA1	73 (0.40)	3.39 (2.17-5.45)	114 (3.00)	26.33 (17.28-41.52)	65 (4.44)	42.88 (26.56-71.25)
BRCA2	201 (1.09)	4.66 (3.52-6.23)	82 (2.16)	8.89 (6.36-12.47)	30 (2.05)	9.70 (5.97 15.47)
CDH1	13 (0.07)	3.37 (1.24-10.72)	3 (0.08)	N/A	1 (0.07)	N/A
CHEK2	205 (1.11)	2.60 (2.05-3.31)	20 (0.53)	1.40 (0.83-2.25)	8 (0.55)	1.63 (0.72 3.20)
*NF1*Δ	10 (0.05)	1.63 (0.65-4.03)	2 (0.05)	N/A	1 (0.07)	N/A
PALB2	64 (0.35)	3.13 (2.02-4.96)	42 (1.10)	9.22 (5.63-15.25)	24 (1.64)	13.03 (7.08-23.75)
PTEN	3 (0.02)	N/A	0	N/A	0	N/A

RAD51C	16 (0.09)	0.83 (0.44-1.54)	9 (0.24)	2.19 (0.97-4.49)	4 (0.27)	N/A
RAD51D	13 (0.07)	1.61 (0.71-3.70)	7 (0.18)	3.93 (1.40-10.29)	1 (0.07)	N/A
TP53[Δ]	9 (0.05)	N/A	2 (0.05)	N/A	2 (0.14)	N/A

ER: estrogen receptor; CI: confidence interval; *ATM*: ataxia-telangiectasia mutated; *BARD1*: *BRCA1*-associated RING domain 1; *BRCA1*: breast cancer susceptibility gene 1; *BRCA2*: breast cancer susceptibility gene 2; *CDH1*: cadherin 1; *CHEK2*: checkpoint kinase 2; *NF1*: neurofibromatosis type 1; *PALB2*: partner and localizer of *BRCA2*; *PTEN*: phosphatase and tensin homolog tumor suppressor gene; *RAD51C*: RAD51 paralog C; *RAD51D*: RAD51 paralog D; *TP53*: tumor protein p53; CARRIERS: Cancer Risk Estimates Related to Susceptibility Consortium; BWHS: Black Women's Health Study; CPSII: Cancer Prevention Study II; CPS3: Cancer Prevention Study-3; CTS: California Teachers' Study; MCBCS: Mayo Clinic Breast Cancer Study; MEC: Multiethnic Cohort Study; MMHS: Mayo Mammography Health Study; NHS: Nurses' Health Study; NHSII: Nurses' Health Study II; WCHS: Women's Circle of Health Study; WHI: Women's Health Initiative; WWHS: Wisconsin Women's Health Study.

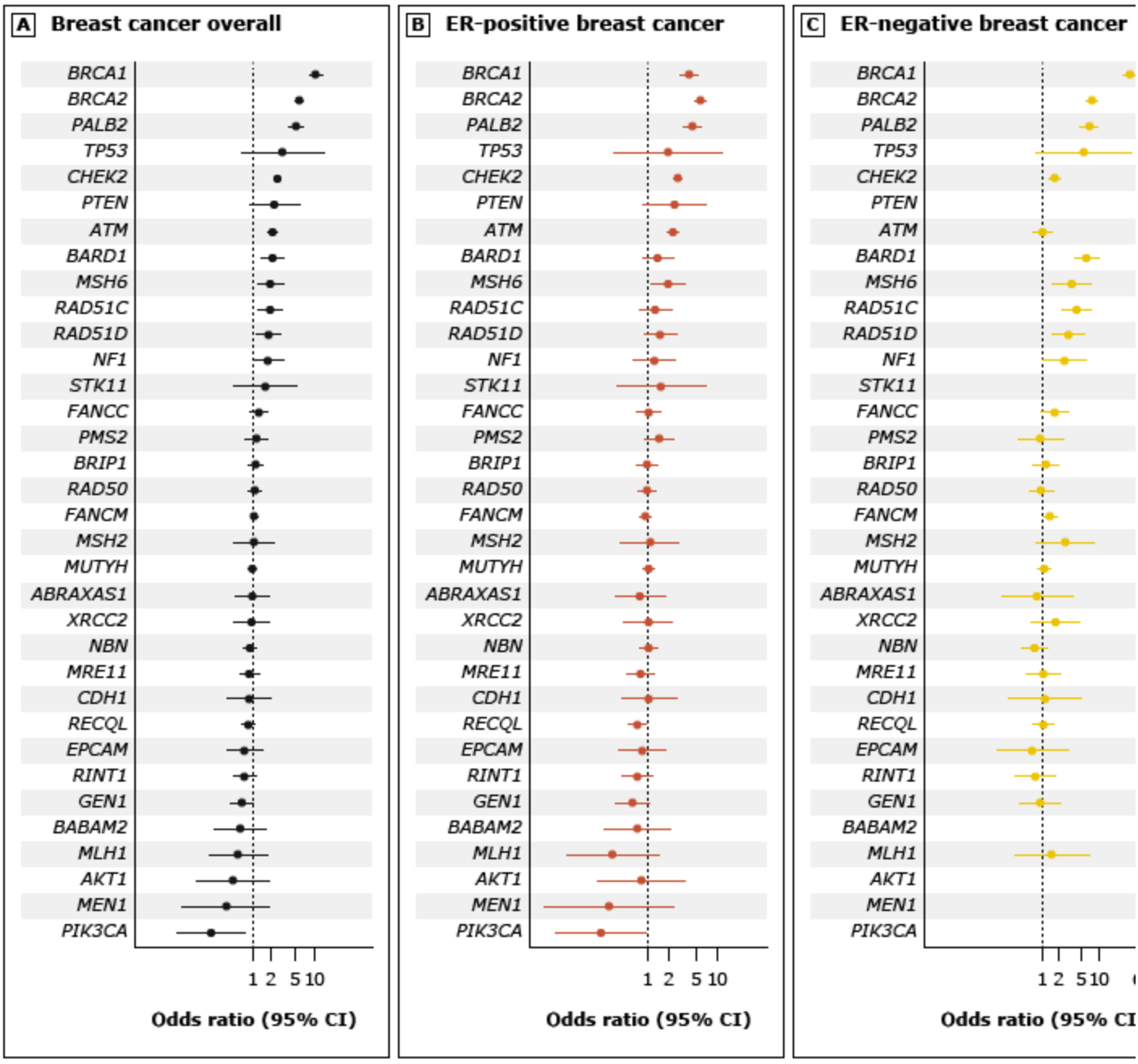
* The studies in the CARRIERS consortium that were included in this population-based analysis were BWHS, CPSII, CPS3, CTS, MCBCS, MEC, MMHS, NHS, NHSII, WCHS, WHI, and WWHS.

¶ Odds ratio estimates for any breast cancer were adjusted for study, age, family history of breast cancer, and race or ethnic group.

Δ Pathogenic variants in *NF1* and *TP53* were restricted to those with an alternate allele fraction between 0.3 and 0.7.

Graphic 131004 Version 2.0

Risk of breast cancer overall and tumor subtypes associated with protein-truncating variants in 34 genes in population-based studies



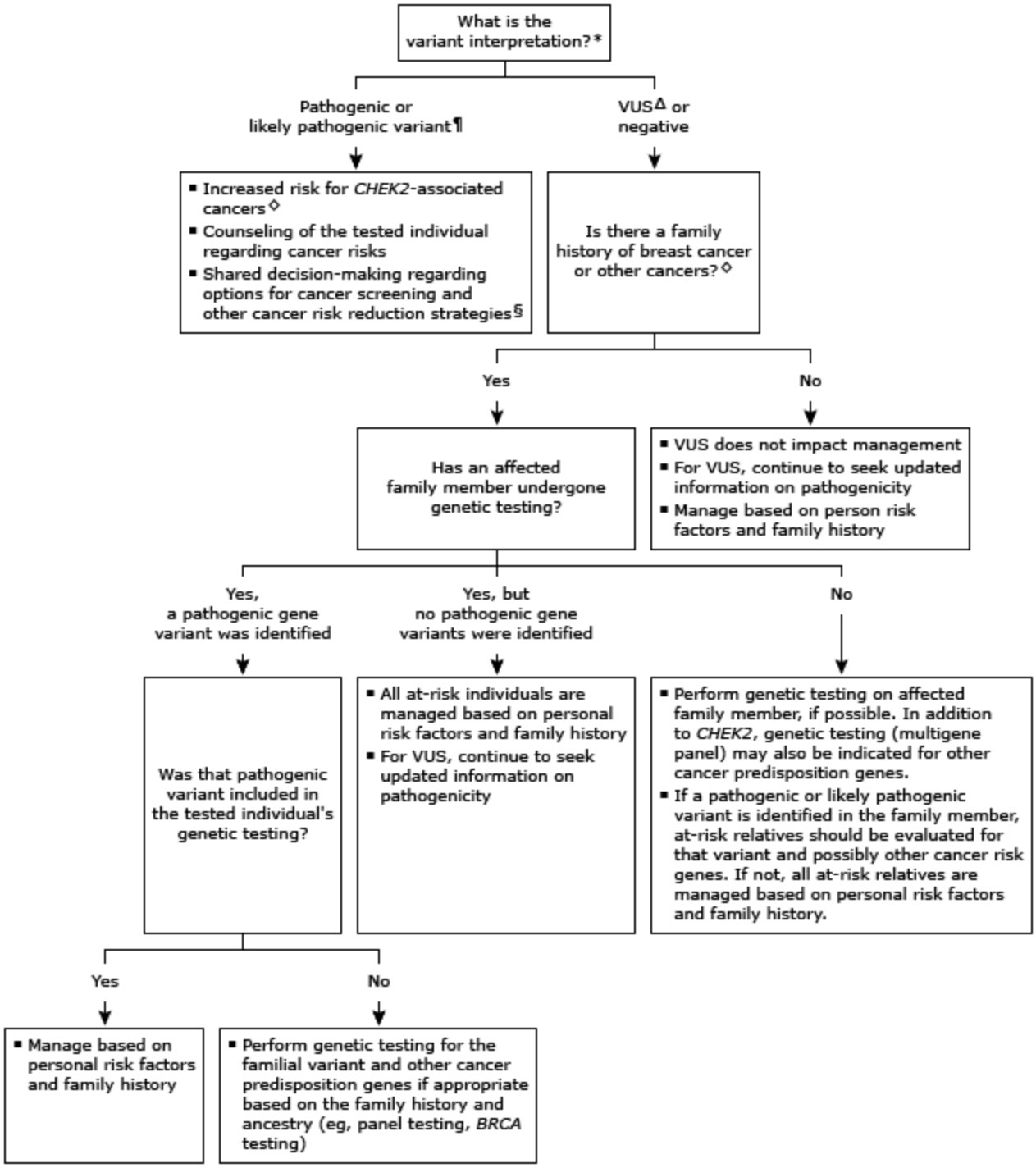
Shown are odds ratios and 95% CIs for breast cancer overall (Panel A), ER-positive breast cancer (Panel B), and ER-negative breast cancer (Panel C) associated with protein-truncating variants in 34 genes. The genes are listed in order of decreasing estimated odds ratios for breast cancer overall.

ER: estrogen receptor; CI: confidence interval.

From: Breast Cancer Association Consortium, Dorling L, Carvalho S, et al. Breast cancer risk genes-association analysis in more than 113,000 women. N Engl J Med 2021; 384:428. Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Graphic 131005 Version 2.0

Germline *CHEK2* genetic test result interpretation in an individual without cancer



This algorithm is only intended for individuals without cancer. Interpretations of pathogenicity may be revised as more data become available. It is especially important to seek this updated information periodically for a VUS.

VUS: variant of uncertain significance.

* Ensure that the genetic testing is performed properly, the patient identification is correct, and the interpretation of pathogenicity is accurate based on the most recent data.

¶ Frameshift/protein truncating pathogenic and likely pathogenic variants (eg, 1100delC) are treated the same for purposes of surveillance and risk reduction interventions. Medical management should be individualized for those with a missense variant (eg, I157T) and those with a family history of cancer.

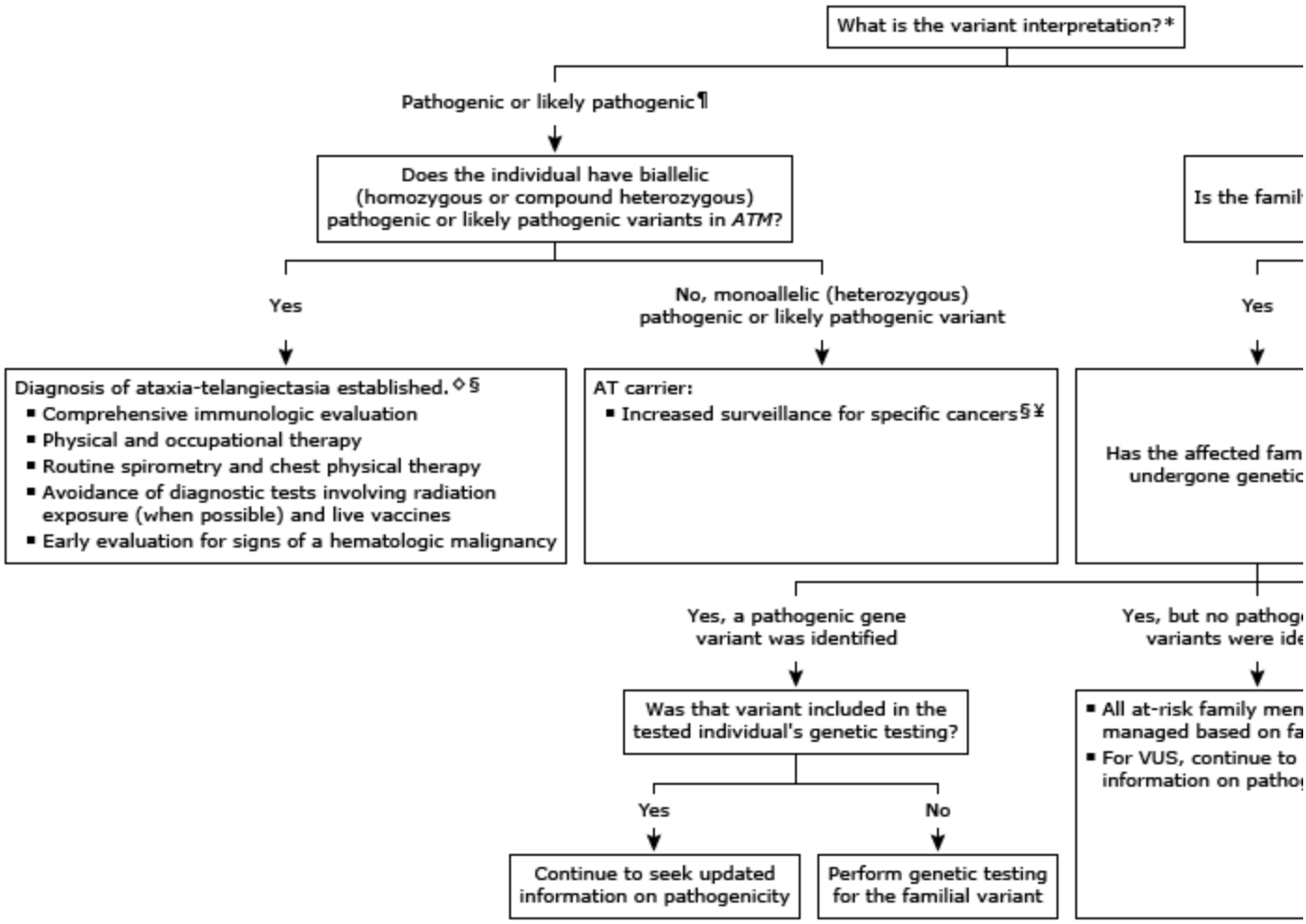
Δ VUS lack sufficient information from clinical and bench research to be classified as pathogenic or benign. Continue to seek updated interpretation of pathogenicity periodically (eg, annually).

◇ *CHEK2* is associated with increased risks for breast cancer (female and male), colorectal cancer, and prostate cancer. Increased risk for other types of cancer have been reported and are difficult to quantify.

§ Refer to related UpToDate content on *CHEK2*.

Graphic 138683 Version 1.0

Germline ataxia-telangiectasia (*ATM* gene) genetic test result



Interpretations of pathogenicity may be revised as more data become available. It is especially important to seek this updated information periodically for a VUS. Discussion with a genetic counselor and/or an expert in hereditary syndromes is likely to be appropriate for most individuals with pathogenic or likely pathogenic variants in the *ATM* gene.

AT: ataxia-telangiectasia; ATM: ataxia-telangiectasia mutated; VUS: variant of uncertain significance.

* Ensure that the genetic testing is performed properly, the patient identification is correct, and the interpretation of pathogenicity is accurate based on the most recent data analysis.

¶ Pathogenic and likely pathogenic variants are treated the same for purposes of surveillance and risk reduction interventions; these interventions are independent of family history.

Δ VUS lack sufficient information from clinical and bench research to be classified as pathogenic or benign. Continue to seek updated interpretation of pathogenicity periodically (eg, annually).

◇ Individuals with AT are at increased risk for cancer during childhood. The majority (85%) are lymphomas and acute leukemias. Among patients who survive to adulthood (>20 years), there also appears to be an increase in the risk of solid tumors as compared with the general population. Refer to

UpToDate for the age at which interventions are initiated, the frequency at which they are performed, and the evidence to support these interventions.

§ Refer to related UpToDate content on ataxia-telangiectasia for additional information.

¥ Those with a single pathogenic variant in *ATM* (AT carriers) are at increased risk for breast cancer, pancreatic cancer, and other solid tumors in adulthood.

Graphic 138554 Version 1.0

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