Current Breast Cancer Reports (2018) 10:209–218
https://doi.org/10.1007/s12609-018-0282-y

RISK AND PREVENTION (ME WOOD, SECTION EDITOR)

# Risk and Prevention for Highly Penetrant Genes

Ami Chitalia[1] · Katia Khoury[2] · Claudine Isaacs[2]

Published online: 9 July 2018


**Abstract**

**Purpose of Review** Approximately 10% of breast cancer cases are attributed to a hereditary predisposition. Here, we review the risks and management options for highly penetrant genes including *BRCA1/2*, *TP53*, *PTEN*, *CDH1*, *STK11*, and *PALB2* which confer a 5 to greater than 10-fold increased risk of breast cancer, and an increased risk of other cancers.

**Recent Findings** Risk-reducing salpingo-oophorectomy (RRSO) reduces mortality in *BRCA1/2* carriers. Other management strategies are tailored to the hereditary cancer syndrome in question and include more intensive screening with imaging and serologic studies, risk-reducing surgeries such as mastectomy, and consideration of risk reduction agents.

**Summary** Given the advances in our knowledge regarding the impact of management strategies in mutation carriers, genetic testing for high-penetrance breast cancer genes has become standard of care. It is critically important to discuss the implications of testing unaffected family members, in order to be able to offer impactful interventions to healthy at-risk individuals.

**Keywords** Highly penetrant genes · Breast cancer · Ovarian cancer · Risk · Screening · Prevention

## Introduction

Breast cancer is the second leading cause of death in women after cardiovascular disease, and over 240,000 cases are diagnosed each year in the USA [1]. Approximately 10% of all cases are attributed to a hereditary predisposition [2, 3], with mutations in the breast cancer type 1 or 2 susceptibility genes (*BRCA1* and *BRCA2*) being the best-characterized causes of hereditary breast cancer. In addition to *BRCA1/2,* a number of other rare high-penetrance genes have also been identified including *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome), *CDH1* (hereditary diffuse gastric cancer), and *STK11* (Peutz-Jeghers syndrome). Mutations in these genes all confer a greater than 10-fold increased risk of breast cancer. *PALB2* is also considered a high-risk gene and is associated with about a 5–10-fold excess risk of breast cancer [4]. More moderate-risk genes, which are associated with about a 2–5-fold excess risk of breast cancer, include *CHEK2*, *ATM*, *BARD1*, *RAD51D*, and *MSH6* [4].

In this article, we will review the cancer risks and management options for healthy individuals who have been found to harbor a mutation in a highly penetrant breast cancer gene. It is important to note that most of the management guidelines are based on expert opinion, as randomized trials are difficult to carry out in these rare high-risk populations. The guidelines are predicated on the risks for cancer as well as the age at which cancer risk begins to rise. Additionally, when considering management options for these high-risk individuals, it is key to consider the differences between screening and prevention. The goal of screening is to detect a cancer at its earliest stage when it is more likely to be curable. The aim of prevention is to decrease the likelihood of ever developing cancer. Finally, decision-making regarding which strategies to pursue should be made on an individual basis, and should consider individual values as they pertain to quality of life as well as other social and psychosocial factors. It is important to note that an individual's decision about which strategy to pursue can change over time.

This article is part of the Topical Collection on *Risk and Prevention*

✉ Claudine Isaacs
isaacsc@georgetown.edu

[1] Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC 20010, USA

[2] Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, 3800 Reservoir Road NW, Washington, DC 20007, USA

## Management of Unaffected BRCA1/2 Mutation Carriers

Data from a number of primarily retrospective studies indicate that *BRCA1* mutation carriers have about a 57–65% risk of

breast cancer and 39–59% risk of ovarian cancer. For *BRCA2* mutation carriers, these risks range from 45 to 57% for breast cancer and 11 to 18% for ovarian cancer [5]. A recently published multi-institutional international prospective cohort study further validated these estimates. This study included 6036 *BRCA1* and 3820 *BRCA2* female mutation carriers and found that the lifetime risk of developing breast cancer by age 80 as 72% for *BRCA1* and 69% for *BRCA2* mutation carriers. The lifetime risk of ovarian cancer was estimated at 44% for *BRCA1* and 17% for *BRCA2* mutation carriers [6]. These cancers also typically occur at a younger age than is seen in the general population, with studies indicating that over 40% of *BRCA1* and 35% of *BRCA2* mutation carriers develop breast cancer by the age of 50. For ovarian cancer, the risk in *BRCA1* mutation carriers begins to rise in their late 30s and 40s whereas for *BRCA2* mutation carriers this rise occurs at age 50 [6]. *BRCA1/2* mutation carriers are also at increased risk of developing fallopian tube cancers, with a lifetime risk of 0.6 versus 0.2% in the general population. It is thought that 50% of serous cancers including ovarian cancers may be arising from the distal fallopian tubes [7, 8].

Mutation carriers also have an increased risk of second breast cancer. Studies indicate up to a 60% risk of developing a contralateral breast cancer. This risk appears to be influenced by the age at diagnosis of the primary breast cancer [9, 10]. The large prospective study described above found a cumulative risk for contralateral breast cancer of 40% for *BRCA1* and 26% for *BRCA2*, 20 years after the first diagnosis [6]. Strength of family history may also impact cancer risks. The prospective cohort analysis found about a 2-fold excess risk of breast cancer over baseline for *BRCA1/2* mutation carriers with two or more first- or second-degree relatives compared to those with no affected relatives [6].

Mutation location has also been shown to play an important role. An observational study of more than 30,000 *BRCA1/2* mutation carriers identified breast cancer and ovarian cancer cluster regions in *BRCA1* and *BRCA2*, with breast and ovarian cancer risks varying by type and location of mutations [11].

Other cancers are also found more frequently in *BRCA1/2* mutation carriers. The risk of male breast cancer is estimated at 7% in *BRCA2* mutation carriers and about 1% in *BRCA1* mutation carriers. This compares to a 0.1% risk in the general population. The typical age of onset is after 60 years of age [12]. Male *BRCA2* mutation carriers have been estimated to have a 2.5- to 9-fold excess risk of prostate cancer and, while there is debate about whether *BRCA1* mutation carriers have an increased risk, some studies have suggested they have up to a 3.75 increase in risk. Additionally, a number of other cancers including pancreatic cancer, melanoma, uterine papillary serous carcinoma, stomach, biliary, and possibly colorectal cancer have been described to be more common in mutation carriers, but the absolute risk of these malignancies is low [5, 13, 14].

## Screening and Prevention Options for Breast Cancer (Table 1)

### Breast Cancer Screening

*BRCA1* and *BRCA2* mutation carriers who have not yet undergone risk-reducing surgery should be counseled on screening strategies as recommended by expert opinion and guidelines such as those issued by NCCN [15]. This includes breast awareness beginning at age 18, clinical breast exam (CBE) every 6 months beginning at age 25, and annual breast MRI for women between the ages 25 to 75. In addition to breast MRI, screening mammography is recommended for ages 30 to 75. If there is a family history of breast cancer under the age of 30, these ages should be adjusted accordingly. A large retrospective cohort study found that any exposure to radiation prior to the age of 30 in *BRCA1/2* mutation carriers was associated with an increased risk of breast cancer [16]. As a result, the age of initiation of annual screening mammography has been changed to begin at age 30. For women aged 75 and older, recommendations should be made on an individual basis.

Although the impact of screening MRI on mortality is unknown, one large prospective study of 445 *BRCA1/2* mutation carriers demonstrated a shift in the stage of diagnosis in those undergoing MRI screening. Mutation carriers undergoing MRI in addition to mammography were significantly more often diagnosed with stage 0 and 1 breast cancer than those undergoing only mammography [17]. The role of breast ultrasound as a screening tool has also been evaluated. A large single-center prospective study done in Austria compared the role of screening breast MRI, mammography, and ultrasound in 559 women who were either *BRCA1/2* mutation carriers or were found to have at least a 20% likelihood of developing breast cancer based on family history criteria [18]. The sensitivity of MRI was significantly higher than mammography and ultrasound, regardless of age, mutation status, or breast density. MRI detected all but two cancers and mammography was the sole detection method for two cases of DCIS with microinvasion. However, no cancers were detected by ultrasound alone. Thus, ultrasound is not a recommended screening modality in *BRCA1/2* mutation carriers. An important consideration is that while MRI is a sensitive test, it can have false-positive findings. In order to minimize false positives, it is recommended that MRI be performed days 7–15 of the menstrual cycle in premenopausal women and by radiologists experienced in breast MRI.

### Breast Cancer Prevention

The options for prevention include both chemoprevention and surgical prophylaxis with either risk-reducing mastectomy (RRM) or risk-reducing salpingo-oophorectomy (RRSO). A

**Table 1** Summary of management recommendations for breast and ovarian cancer for *BRCA1/2* mutation carriers

| | Breast cancer | Ovarian Cancer |
|---|---|---|
| Screening | CBE every 6–12 months beginning at age 25<br>Breast MRI annually ages 25 to 75<br>Mammogram annually ages 30 to 75<br>Individualize screening after age 75 | Transvaginal ultrasound and CA-125 every 6 months, ages 30 to 35 can be considered |
| Prevention | Bilateral mastectomy based on personal preference<br>Bilateral salpingo-oophorectomy at age 35–40 for BRCA1 carriers, and age 40–45 for BRCA2 carriers<br>Consider risk reduction agents | Bilateral salpingo-oophorectomy at age 35–40 for BRCA1 carriers, and age 40–45 for BRCA2 carriers is strongly recommended<br>Consider risk reduction agents |

number of studies have evaluated the role of RRM including a prospective study of 358 high-risk women (including 236 *BRCA1/2* mutation carriers) who had undergone RRM [19]. In this study, after 4.5 years of follow-up, there were no primary breast cancers diagnosed in the RRM group; there was one metastatic breast cancer diagnosed 4 years after RRM in a woman who did not have a previously known primary breast cancer. Additionally, a large prospective multi-center study of over 2400 *BRCA1* or *BRCA2* mutation carriers evaluated the impact of RRM and RRSO on breast and ovarian cancer risk [20]. In this study, with about 3 years follow-up, no breast cancers were diagnosed in women who underwent RRM (0 of 247) as opposed to 7% of women who did not (98 of 1372). Finally, a meta-analysis which included 10 studies of *BRCA1/2* mutation carriers undergoing RRM found a 90 to 100% reduction in risk of breast cancer incidence [21]. However, no benefit in overall survival has been reported, perhaps because the follow-up has not been long enough. Based on the data presented, expert guidelines strongly recommend considering RRM for breast cancer prevention in *BRCA1/2* mutation carriers. However, it is important to have individualized discussions regarding this recommendation and to fully consider the psychosocial impact and morbidity of this procedure. A prospective study of 90 women who had undergone RRM evaluated issues surrounding anxiety, depression, sexuality, and body image by questionnaires done prior to, 6 months after, and 12 months after surgery [22]. Although anxiety did decrease by 12 months after surgery, almost half of the women reported problems with body image and sexual pleasure decreased compared to prior to surgery.

With advances in surgical techniques, many mutation carriers are now routinely being offered nipple-sparing mastectomy. A recent retrospective study reviewed the outcomes of nine large institutions' experience with prophylactic nipple-sparing mastectomy. In their series, 202 mutation carriers underwent bilateral RRM and 144 had unilateral RRM following a diagnosis of contralateral breast cancer. They found no cases of primary breast cancer in either group (mean follow-up of 34 and 56 months, respectively), whereas based on modeling, 22 would have been expected [23]. These results are encouraging in terms of superior cosmetic outcomes with nipple-sparing mastectomy, which may result in improvements in body image and preservation of sexual function.

In addition to RRM, RRSO can also be considered as a means to reduce breast cancer risk and mortality in *BRCA1/2* mutation carriers. In the prospective multi-institution study discussed above, 993 mutation carriers underwent RRSO [20]. When compared to those who had not undergone this procedure, RRSO was associated with about a 50% reduction in breast cancer risk in those without a previous diagnosis of breast cancer. When breast cancer risk reduction was stratified by mutation carrier type, there was a 37% relative risk reduction amongst *BRCA1* mutation carriers and 64% amongst *BRCA2*. This difference may be because more *BRCA2*-associated breast cancers are estrogen receptor positive, though further investigation is needed. Furthermore, the effect was age dependent, with no effect seen after age 50. A second case-control study of 1439 *BRCA1*/*BRCA2* mutation carriers with breast cancer matched to 1866 carriers without breast cancer found that oophorectomy was associated with a 57 and 46% reduction in breast cancer risk for *BRCA1* and *BRCA2* mutation carriers, respectively [24]. Of note, the risk reduction was greater when surgery was performed at less than 40 years of age. More recently, however, studies have suggested that RRSO may not reduce breast cancer risk in *BRCA1* mutation carriers in particular. In a study by the Dutch Hereditary Breast Cancer Registry that included 822 mutation carriers, 246 *BRCA1* and 100 *BRCA2* mutation carriers opted for RRSO [25]. Analyses were conducted to attempt to limit cancer-induced testing bias and immortal person-time bias—which involved including participants who did not have a known breast or ovarian cancer diagnosis prior to their mutation testing, and taking into account person-time bias before RRSO—and concluded that RRSO had no significant effect on breast cancer incidence (12.1% in non-RRSO vs. 9.9% in RRSO group, $p = 0.31$). However, the authors did find a trend toward a lower breast cancer risk in premenopausal mutation carriers who underwent RRSO, particularly in *BRCA2* mutation carriers. There were some limitations to this study, including that the average age of women undergoing RRSO was 44 years, while that of the non-RRSO group was significantly younger, at 33 years. Given the age

differential, the non-RRSO group had a lower absolute risk of breast cancer. Conversely, there was little time left to see any potential impact on breast cancer risk of the group undergoing RRSO, as the average age was close to that of natural menopause. In response to this analysis, a re-analysis was conducted of data from two previous publications reporting positive findings of RRSO and breast cancer risk reduction [26]. The immortal person-time bias was taken into account during the re-analysis and still resulted in hazard ratios similar to those previously reported, indicating a protective effect of RRSO on breast cancer risk in mutation carriers. A more recent international prospective study looked at over 3700 *BRCA1/2* mutation carriers, of which 1552 underwent RRSO either before or after study enrollment [27]. A total of 350 new primary breast cancers were diagnosed over a median follow-up of over 5 years; 40.9% of these occurred in those who had previously undergone RRSO. The annual incidence of breast cancer in those with and without RRSO was similar and did not vary between *BRCA1* and *BRCA2* mutation carriers. RRSO was associated with a statistically significant breast cancer risk reduction in *BRCA2* mutation carriers under the age of 50. However, this was not seen in *BRCA1* mutation carriers under the age of 50. Due to the conflicting data, there is still debate regarding the impact of RRSO on breast cancer prevention.

When considering RRSO prior to the natural age of menopause, the potential symptoms and risks of this procedure should also be taken into account. In an effort to mitigate these effects, the role of hormone replacement therapy (HRT) post-RRSO has been evaluated. A prospective study found that mutation carriers who took HRT post-RRSO had about a 45% reduction in risk of developing breast cancer, a benefit very similar to those who did not take HRT post-RRSO [28]. The study did not take into account the type or duration of HRT use, but does suggest that short-term HRT cancer be safely offered post-RRSO.

In addition to surgical prophylaxis, chemoprevention can also be considered for breast cancer prevention. Little data exists on primary chemoprevention with either selective estrogen receptor modulators (SERMs) such as tamoxifen or aromatase inhibitors (AIs) in *BRCA1/2* mutation carriers. However, an international study of over 2400 *BRCA1/2* mutation carriers with a diagnosis of unilateral breast cancer demonstrated that treatment with tamoxifen decreased the risk of contralateral breast cancer both in *BRCA1* and *BRCA2* mutation carriers, suggesting that this therapy may have benefit [29]. Since *BRCA1* mutation carriers tend to develop triple negative cancers, questions have been raised regarding tamoxifen effectiveness as a chemoprevention agent in this group of women. In general, tamoxifen can be considered for primary risk reduction in *BRCA2* mutation carriers who opt against RRM, although data is limited [30]. Due to limited and conflicting data, the NCCN does not currently recommend consideration of chemoprevention with tamoxifen [15].

## Ovarian Cancer Screening and Prevention (Table 1)

### Ovarian Cancer Screening

NCCN guidelines no longer routinely recommend routine screening for ovarian cancer, as studies have yet to show benefit. However, transvaginal ultrasound and serum CA-125 level every 6 months beginning at age 30, or earlier depending on family history, can be considered [15]. False positives can be minimized by performing these tests in the first half of the menstrual cycle; it is important to note that CA-125 levels can be higher in premenopausal compared to post-menopausal women. Trials implementing the risk of ovarian cancer algorithm (ROCA), which follows the change in CA-125 over time from baseline, suggest it may have a benefit in positive predictive value of early-stage ovarian cancer compared to utilizing the single cut-off of 35 U/mL for CA-125 levels [31].

### Ovarian Cancer Prevention

When considering prevention for ovarian cancer, the modalities again include surgical prophylaxis or chemoprevention. With respect to surgical prophylaxis, the international study discussed above included 1557 mutation carriers unaffected by cancer and demonstrated that those undergoing RRSO had about a 70% reduction in risk of ovarian cancer and a 55% reduction in all-cause mortality [20]. A second large prospective study of over 5700 mutation carriers found an 80% risk reduction of ovarian cancer with RRSO as well as a 77% reduction in all-cause mortality at age 70 in those undergoing RRSO [32]. Given the significant impact on cancer incidence and even more importantly on mortality, current guidelines strongly recommend RRSO. The NCCN guidelines recommend RRSO for *BRCA1* mutation carriers between ages 35 and 40, and upon completion of childbearing [15]. Because the onset of ovarian cancer in *BRCA2* mutation carriers tends to be 8 to 10 years later, RRSO can be delayed to ages 40 to 45 years in this population. As many of the ovarian cancers are thought to originate in the distal fallopian tubes, the possibility of delaying RRSO until the age of natural menopause and performing bilateral salpingectomy alone post-childbearing has arisen. The effectiveness of this method is still being studied and thus this should not be offered as a standard of care. Furthermore, it would not provide the breast cancer risk reduction that is achieved with premenopausal oophorectomy.

The role of risk-reducing hysterectomy in mutations carriers is also controversial. A large study of over 4000 mutation carriers found a cumulative risk of endometrial cancer of 2.8% by age 75; the risk in tamoxifen users was higher at 4.3% [33]. A more recent prospective study looked at over 1000 mutation carriers who had undergone RRSO without hysterectomy [34] and found that although there was no overall increased risk of endometrial cancers, there were four cases of serous-like

endometrial cancers in *BRCA1* compared to one in *BRCA2* mutation carriers. Given the low absolute risk of endometrial cancer in *BRCA1/2* mutation carriers, it is not currently recommended that hysterectomy be performed solely for risk reduction.

Two separate meta-analyses of retrospective and case-control studies have looked at the impact of oral contraceptive pill (OCP) use on cancer risk in mutation carriers and found that they reduce the risk of ovarian cancer [35, 36]. However, it was noted that OCP use may be associated with a slight increased risk of breast cancer, or shift the age of onset downwards. An abstract presented at AACR in 2017 from three large hereditary cancer cohorts which included over 5000 *BRCA1* and 3000 *BRCA2* mutation carriers was not able to clearly determine if OCP use was associated with an increased risk of breast cancers [37]. Given the lack of high-quality data, OCP use can be considered for prevention of ovarian cancer in mutation carriers, though it is not a standard recommendation. Furthermore, the potential for increase in risk of breast cancer must be considered. In addition, the recommended age for RRSO is typically prior to the age at which mutation carriers are at highest risk of ovarian cancer, making the benefit of OCP unclear.

### Other Cancers

Male mutation carriers should begin breast self-exam and CBE at age 35. There is only limited data regarding breast imaging in male carriers and breast imaging is not recommended by the current guidelines [15].

Given the increased risk of prostate cancers, studies have also evaluated the role of PSA screening in men with a known genetic predisposition to prostate cancer secondary to *BRCA1/2* mutations. The IMPACT study recently reported results of PSA velocity screening in 584 *BRCA2* mutation carriers, 510 *BRCA1* mutation carriers, and 548 family members who had tested negative for the *BRCA* mutation. A total of 174 individuals with three or more PSA readings underwent a prostate biopsy, and 45 were diagnosed with prostate cancer. They found that PSA was more strongly predictive of prostate cancer in *BRCA1/2* mutation carriers than non-carriers, and found no further benefit from incorporating PSA velocity [38]. NCCN guidelines recommend prostate cancer screening beginning at age 45 in *BRCA2* mutation carriers, and that such screening be considered in *BRCA1* mutation carriers [15].

There are no specific guidelines for screening for pancreatic cancer or melanoma, but screening should be individualized, based on family history.

## Management of Other High-Risk Hereditary Breast Cancer Syndromes (Table 2)

Given the advent of panel testing, increasing numbers of individuals are being identified as carrying a deleterious mutation in another high-penetrance gene. We will review the known cancer risks associated with mutations in these high-penetrance genes as well as their current management strategies. Of note, the cancer risk and management guidelines are based on findings from high-risk families identified by phenotype directed testing. Because of this ascertainment bias, it is unclear if the cancer risks and hence management strategies for patients identified through multigene panel testing (without features of the associated syndrome) will be the same as those quoted in the literature.

### Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is associated with an autosomal dominant mutation in the tumor protein p53 (*TP53*) tumor suppressor gene. Mutation carriers have a lifetime cancer risk of about 90% for women and 70% for men. The most frequently associated cancer is breast cancer, with studies indicating about a 70% lifetime risk. Other hallmark cancers include but are not limited to sarcomas (about 25% of tumors), brain tumors including choroid plexus carcinomas (which tend to occur even in the absence of family history or other cancers), adrenocortical cancer, and leukemia. It is now also known as the sarcoma, breast, leukemia, and adrenal gland (SBLA) cancer syndrome. LFS is also notable for childhood cancers, multiple primary cancers, and an increased risk of secondary cancers within a radiation treatment field [39]. Breast cancers associated with LFS are frequently associated with amplification of HER2, bilateral breast cancers, and a younger age of onset with studies showing median age of onset at 33–37 [39–42]. One report of 12 families with LFS identified one third of breast cancers before age 30 [43].

Current NCCN guidelines for *TP53* mutation carriers recommend breast cancer screening including breast awareness beginning at age 18, CBE every 6–12 months starting at age 20 to 25 or 5 to 10 years before the first breast cancer in family, annual MRI between ages 20 to 29, and then annual mammogram in addition to annual MRI between ages 30 to 75 [15]. In addition, it is appropriate to consider RRM for these women. A recently published long-term prospective study found that a comprehensive surveillance protocol, which included annual whole-body, brain and breast MRI, annual mammography, and abdominal and pelvic ultrasound every 3–4 months, as well as colonoscopy, statistically significantly improved long-term survival [44]. In this study of 89 *TP53* mutation carriers, 40 initially agreed to surveillance and 49 declined; of those who declined, 19 ended up crossing over to the surveillance arm. Forty asymptomatic tumors were diagnosed in 19 of the 59 patients who underwent surveillance, while 61 symptomatic tumors were diagnosed in 43 of the patients who initially declined surveillance. Those who underwent surveillance had a 5-year overall survival of close to 90% compared to about 60% for those who did not ($p = 0.01$). A more recent

**Table 2** Management options for high-risk hereditary breast cancer mutations

| High-risk gene (associated syndrome) | Lifetime breast cancer risk | Breast cancer screening and prevention |
|---|---|---|
| *TP53* (Li-Fraumeni) | ~90% | -CBE every 6–12 months beginning at age 20–25 or 5–10 years before first cancer in family<br>-Annual MRI beginning at ages 20<br>-Annual mammogram between ages 30 to 75<br>-Consider RRM |
| *PTEN* (Cowden/*PTEN* hamartoma) | 25–85% | -CBE every 6–12 months beginning at age 20–25 years or 5–10 years before first cancer in family<br>-Annual mammogram and MRI starting between ages 30–35<br>-Consider RRM |
| *STK11* (Peutz-Jeghers) | ~45–57% | -CBE every 6 months<br>-Annual mammogram and MRI starting at age 25<br>-Consider RRM based on family history |
| *CDH1* (hereditary diffuse gastric cancer) | ~40% | -Annual mammogram and consider annual breast MRI starting at age 30<br>-Consider RRM based on family history |
| *PALB2* | 35–50% | -Annual mammogram and consider annual breast MRI starting at age 30<br>-Consider RRM based on family history |

meta-analysis assessed the clinical utility of whole-body MRI in germline *TP53* mutation carriers: of 578 individuals, 42 cancers were identified on the baseline scan in 39 individuals, 35 cancers of which were treated with curative intent. The overall estimated detection rate for new, localized primary cancers was 7%. The majority of cohorts included the brain as part of the whole-body MRI. Out of 10 brain tumors identified in individuals undergoing both brain and whole-body MRI, only 5 of them were diagnosed on the whole-body MRI. Hence, whole-body MRI is not reliable in identifying brain tumors and dedicated brain MRI should be considered in the appropriate clinical setting [45]. Therefore, additional screening for *TP53* mutation carriers should include annual dermatologic and neurologic exams, consideration of colonoscopy every 2–5 years starting at age 25, avoidance of therapeutic radiation, and annual brain and whole-body MRI. If whole-body MRI is not available, individuals are encouraged to participate in clinical trials which utilize it, or pursue alternate comprehensive imaging [15]. Additional surveillance should be considered based on individual family history. Furthermore, as data are accumulating regarding various screening strategies, it is likely that the current recommendations will evolve over time.

## Cowden/PHT Syndrome

Cowden syndrome, or *PTEN* hamartoma tumor syndrome (PHTS), is associated with a constellation of symptoms which can include mucocutaneous lesions (trichilemmomas, acral keratosis, and facial papules) and macrocephaly, as well as high-risk benign and malignant tumors of the breast, thyroid, endometrium, colon, and kidney. A systematic review in 2013 has re-defined the diagnostic criteria for Cowden syndrome, excluding benign breast disease, uterine fibroids, or genitourinary malformations, and including autism spectrum disorders, colon cancer, and renal cell carcinoma [46]. Cowden syndrome has traditionally been associated with an autosomal dominant mutation of the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene. However, a number of individuals with Cowden syndrome have tested negative for *PTEN* mutations, and alterations in other genes such as such as *SDHx*, *KLLN*, *AKT1*, and *PIK3CA* have been identified, suggesting that these genes may be associated with Cowden syndrome [47].

Lifetime risk of breast cancer had traditionally been estimated at 25 to 50%. However, recent studies suggest this risk may be as high as 67–85% [47]. Several studies have also described a high risk of second breast cancers in *PTEN* mutation carriers, up to 29% within 10 years from the first diagnosis [48]. A study of over 3000 individuals who met relaxed International Cowden Consortium operational criteria for Cowden syndrome identified 368 patients with a pathogenic germline *PTEN* mutation [49]. The estimated lifetime risks of invasive cancer were 85% for breast cancer (with 50% penetrance by 50 years of age), 35% for epithelial thyroid cancer, 34% for kidney cancer, 28% for endometrial cancer, 9% for colorectal cancer, and 6% for melanoma. Breast cancers began to occur at age 30 and endometrial cancer at age 25. Other

recent studies from groups in the Netherlands and France have found similar cancer spectrums, but the risk of renal and skin cancers were not as elevated as in the latter study [50, 51]. A higher incidence of secondary cancers of the thyroid, endometrium, kidney, and colon has also been observed in individuals with Cowden syndrome [48]. Current NCCN guidelines recommend breast cancer screening for female mutation carriers including breast awareness beginning at age 18, CBE every 6–12 months starting at age 20 to 25 or 5 to 10 years before the first breast cancer in family, annual mammogram, and MRI starting at age 30 to 35 or individualized based on earliest breast cancer in family. Annual random endometrial biopsy and/or ultrasound at age 30 to 35 can be considered for endometrial cancer screening in addition to risk-reducing mastectomy and hysterectomy for prevention [15, 47, 48]. Recommendations for screening of other cancers include annual physical exam including thyroid exam beginning at age 18 or 5 years prior to youngest cancer in the family, annual thyroid ultrasound, colonoscopy at least every 5 years beginning at age 35, and consideration for renal ultrasound every 1 to 2 years starting at age 40, dermatologic exam, and psychomotor assessment [15].

### Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is a rare disease associated with a mutation in serine/threonine kinase 11 gene (*STK11*) and is associated with mucocutaneous pigmented lesions and hamartomatous polyps [30]. It carries a breast cancer risk of 45% and gastrointestinal cancer risk of 57% by age 70 [52]. It also carries an increased risk of ovarian, testicular, and lung cancers. In terms of breast cancer risk management, NCCN guidelines recommend CBE every 6 months and annual mammogram and breast MRI, both beginning at age 25. It is felt that there is insufficient evidence regarding the role of RRM. There is also between a 10–40% lifetime risk of various gastrointestinal cancers. Current NCCN guidelines recommend upper and lower endoscopy every 2–3 years beginning in teenage years, baseline CT or MRI enterography by 8 to 10 years with follow-up based on findings but at least by 18 years and then every 2–3 years, and MRCP or EUS every 1–2 years. Additionally, annual pelvic exam beginning at 18–20 years with Pap smear and consideration of transvaginal ultrasound, and testicular exam beginning at 10 years is recommended due to the elevated risk of ovarian, cervical, and testicular cancers. No specific screening measures are currently recommended for lung cancer risk other than smoking cessation [53].

### Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer is due to cadherin-1 (*CDH1*) gene mutations and is associated with a lifetime cumulative gastric cancer risk of 67% in men and 83% in women. It is also associated with a lifetime breast cancer risk of 39%, specifically lobular cancers [54]. In regard to increased risk of breast cancer, NCCN guidelines recommend annual mammogram and consideration of annual breast MRI beginning at age 30. For the increased risk of gastric cancer, prophylactic gastrectomy is recommended between ages 18 to 40; it can be considered under the age of 18 for those with a family member diagnosed with gastric cancer prior to the age of 25. Surveillance with upper endoscopy with random biopsies should be offered every 6 to 12 months for those who decline prophylactic gastrectomy [55]. It is important to note that the recommendations regarding gastric cancer screening and prevention are based on the cancer risks derived from families with high incidences of cancers. It is unclear if these guidelines apply to individuals identified through multigene panel testing, whose personal and family history are not suggestive of this syndrome.

### *PALB2*

*PALB2* is a high-risk breast cancer susceptibility gene and the function of this gene is crucial for *BRCA2* DNA damage responses. Biallelic mutations in *PALB2* cause Fanconi anemia. Monoallelic mutations in *PALB2* are present in a small number of breast cancer patients [30]. One study, which included 362 members of families with a known *PALB2* deleterious mutation, demonstrated a 14% cumulative breast cancer risk by age 50 and 35% by age 70 [56]. *PALB2* mutations also appear to be influenced by the strength of the family history of breast cancer. For instance, the breast cancer lifetime risk in *PALB2* mutation carriers without a family history of breast cancer was 33% whereas in those with two or more close relatives the risk was 58% [40, 56]. This risk is similar to that of *BRCA2* mutation carriers. Additionally an increased risk of bilateral breast cancer has been seen [40]. Current guidelines recommend mammography and breast MRI beginning at 30 years. In addition, RRM should be considered. While some studies suggest that there may be an increased risk of pancreatic or ovarian cancer, currently it is felt that there is insufficient evidence for screening or prevention of these cancers [15].

## Conclusion

Individuals who inherit mutations in high-penetrance genes face markedly elevated risks of breast and ovarian cancers as well as other cancers. For *BRCA1* and *BRCA2* mutation carriers, risk-reducing salpingo-oophorectomy has been demonstrated to reduce overall mortality and is strongly recommended. Other management options depend on the hereditary cancer syndrome and the attendant cancer risks. They include more intensive surveillance with imaging and serological testing or other prevention options including risk-reducing

mastectomy. The majority of management guidelines are based on expert opinion and are likely to evolve as further data accumulate. It is critically important to discuss the therapeutic, social, and psychosocial implications of genetic testing on affected individuals and their at-risk family members, in order to aid in an individualized approach to management.

**Acknowledgements** Lombardi Cancer Center at MedStar Georgetown University Hospital receives research funding from Tesaro for an investigator-initiated trial Dr. Claudine Isaacs co-leads.

## Compliance with Ethical Standards

**Conflict of Interest** Claudine Isaacs serves as consultant for Pfizer and Astra Zeneca.

Ami Chitalia and Katia Khoury declare that they have no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7–30. https://doi.org/10.3322/caac.21332.
2. Foulkes WD. Inherited susceptibility to common cancers. N Engl J Med. 2008;359(20):2143–53. https://doi.org/10.1056/NEJMra0802968.
3. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian ovarian Cancer study group. J Clin Oncol. 2012;30:2654–63. https://doi.org/10.1200/JCO.2011.39.8545.
4. Couch, Fergus. SABCS 2016.
5. Peshkin BN, Isaacs C (2018). Prevalence of BRCA1 and BRCA2 mutations and associated cancer risks. In T. W. Post (Ed.), *UpToDate*. Retrieved from http://www.uptodate.com
6. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast Cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317:2402–16. https://doi.org/10.1001/jama.2017.7112.
7. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002;94(18):1365–72.
8. Aziz S, Kuperstein G, Rosen B, Cole D, Nedelcu R, McLaughlin J, et al. A genetic epidemiological study of carcinoma of the fallopian tube. Gynecol Oncol. 2001;80(3):341–5.
9. Curtis RE, Ron E, Hankey BF, Hoover RN. New malignancies following breast cancer. In: Curtis RE, Freedman DM, Ron E, et al (editors). 2006, pages 189–214.
10. Malone KE, Begg CB, Haile RW, Borg A, Concannon P, Tellhed L, et al. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol. 2010;28(14):2404–10. https://doi.org/10.1200/JCO.2009.24.2495.
11. Rebbeck TR, Mitra N, Wan F, Sinilnikova OM, Healey S, McGuffog L, Mazoyer S, Chenevix-Trench G, Easton DF, Antoniou AC, Nathanson KL, CIMBA Consortium., Laitman Y, Kushnir A, Paluch-Shimon S, Berger R, Zidan J, Friedman E, Ehrencrona H, Stenmark-Askmalm M, Einbeigi Z, Loman N, Harbst K, Rantala J, Melin B, Huo D, Olopade OI, Seldon J, Ganz PA, Nussbaum RL, Chan SB, Odunsi K, Gayther SA, Domchek SM, Arun BK, Lu KH, Mitchell G, Karlan BY, Walsh C, Lester J, Godwin AK, Pathak H, Ross E, Daly MB, Whittemore AS, John EM, Miron A, Terry MB, Chung WK, Goldgar DE, Buys SS, Janavicius R, Tihomirova L, Tung N, Dorfling CM, van Rensburg E, Steele L, Neuhausen SL, Ding YC, Ejlertsen B, Gerdes AM, Hansen Tv, Ramón y Cajal T, Osorio A, Benitez J, Godino J, Tejada MI, Duran M, Weitzel JN, Bobolis KA, Sand SR, Fontaine A, Savarese A, Pasini B, Peissel B, Bonanni B, Zaffaroni D, Vignolo-Lutati F, Scuvera G, Giannini G, Bernard L, Genuardi M, Radice P, Dolcetti R, Manoukian S, Pensotti V, Gismondi V, Yannoukakos D, Fostira F, Garber J, Torres D, Rashid MU, Hamann U, Peock S, Frost D, Platte R, Evans DG, Eeles R, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Hodgson S, Morrison PJ, Walker L, Porteous ME, Kennedy MJ, Izatt L, Adlard J, Donaldson A, Ellis S, Sharma P, Schmutzler RK, Wappenschmidt B, Becker A, Rhiem K, Hahnen E, Engel C, Meindl A, Engert S, Ditsch N, Arnold N, Plendl HJ, Mundhenke C, Niederacher D, Fleisch M, Sutter C, Bartram CR, Dikow N, Wang-Gohrke S, Gadzicki D, Steinemann D, Kast K, Beer M, Varon-Mateeva R, Gehrig A, Weber BH, Stoppa-Lyonnet D, Sinilnikova OM, Mazoyer S, Houdayer C, Belotti M, Gauthier-Villars M, Damiola F, Boutry-Kryza N, Lasset C, Sobol H, Peyrat JP, Muller D, Fricker JP, Collonge-Rame MA, Mortemousque I, Nogues C, Rouleau E, Isaacs C, de Paepe A, Poppe B, Claes K, de Leeneer K, Piedmonte M, Rodriguez G, Wakely K, Boggess J, Blank SV, Basil J, Azodi M, Phillips KA, Caldes T, de la Hoya M, Romero A, Nevanlinna H, Aittomäki K, van der Hout A, Hogervorst FB, Verhoef S, Collée JM, Seynaeve C, Oosterwijk JC, Gille JJ, Wijnen JT, Gómez Garcia EB, Kets CM, Ausems MG, Aalfs CM, Devilee P, Mensenkamp AR, Kwong A, Olah E, Papp J, Diez O, Lazaro C, Darder E, Blanco I, Salinas M, Jakubowska A, Lubinski J, Gronwald J, Jaworska-Bieniek K, Durda K, Sukiennicki G, Huzarski T, Byrski T, Cybulski C, Toloczko-Grabarek A, Złowocka-Perłowska E, Menkiszak J, Arason A, Barkardottir RB, Simard J, Laframboise R, Montagna M, Agata S, Alducci E, Peixoto A, Teixeira MR, Spurdle AB, Lee MH, Park SK, Kim SW, Friebel TM, Couch FJ, Lindor NM, Pankratz VS, Guidugli L, Wang X, Tischkowitz M, Foretova L, Vijai J, Offit K, Robson M, Rau-Murthy R, Kauff N, Fink-Retter A, Singer CF, Rappaport C, Gschwantler-Kaulich D, Pfeiler G, Tea MK, Berger A, Greene MH, Mai PL, Imyanitov EN, Toland AE, Senter L, Bojesen A, Pedersen IS, Skytte AB, Sunde L, Thomassen M, Moeller ST, Kruse TA, Jensen UB, Caligo MA, Aretini P, Teo SH, Selkirk CG, Hulick PJ, Andrulis I Association of type and location of *BRCA1* and *BRCA2* mutations with risk of breast and ovarian cancer. JAMA 2015;313(13):1347–1361. doi: https://doi.org/10.1001/jama.2014.5985.
12. Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2007;99(23):1811–4.
13. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91(15):1310–6.
14. Levine DA, Argenta PA, Yee CJ, Marshall DS, Olvera N, Bogomolniy F, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol. 2003;21(22):4222–7.
15. NCCN Practice Guidelines Hereditary Breast and/or Ovarian Cancer v.1.2018.
16. Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Noguès C. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-

RAD-RISK). BMJ. 2012;345:e5660. https://doi.org/10.1136/bmj.e5660.
17. Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. J Clin Oncol. 2011;29(13):1664–9. https://doi.org/10.1200/JCO.2009.27.0835.
18. Riedl CC, Luft N, Bernhart C, Weber M, Bernathova M, Tea MK, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol. 2015;33(10):1128–35. https://doi.org/10.1200/JCO.2014.56.8626.
19. Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB, van Geel AN, Tilanus-Linthorst MM, Bartels CC, et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. Ann Surg Oncol. 2007;14(12):3335–44.
20. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304(9):967–75. https://doi.org/10.1001/jama.2010.1237.
21. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL, et al. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. Am J Surg. 2016;212(4):660–9. https://doi.org/10.1016/j.amjsurg.2016.06.010.
22. Brandberg Y, Sandelin K, Erikson S, Jurell G, Liljegren A, Lindblom A, et al. Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. J Clin Oncol. 2008;26(24):3943–9. https://doi.org/10.1200/JCO.2007.13.9568.
23. Jakub JW, Peled AW, Gray RJ, Greenup RA, Kiluk JV, Sacchini V, et al. Oncologic safety of prophylactic nipple-sparing mastectomy in a population with BRCA mutations: a multi-institutional study. JAMA Surg. 2018;153(2):123–9. https://doi.org/10.1001/jamasurg.2017.3422.
24. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. 2005;23(30):7491–6.
25. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collée JM, van Doorn HC, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst. 2015;107(5) https://doi.org/10.1093/jnci/djv033.
26. Chai X, Domchek S, Kauff N, Rebbeck T, Chen J. RE: breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst. 2015;107(9) https://doi.org/10.1093/jnci/djv217.
27. Kotsopoulos J, Huzarski T, Gronwald J, Singer CF, Moller P, Lynch HT, et al. Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2016;109(1):djw177. https://doi.org/10.1093/jnci/djw177.
28. Domchek SM, Friebel T, Neuhausen SL, Lynch HT, Singer CF, Eeles RA, Isaacs C, Tung NM, Ganz PA, Couch FJ, Weitzel JN, Olopade OI, Rubinstein WS, Tomlinson GE, Pichert GC, Daly MB, Matloff ET, Evans DG, Garber JE, Rebbeck TR, PROSE Consortium Is hormone replacement therapy (HRT) following risk-reducing salpingo-oophorectomy (RRSO) in BRCA1 (B1)- and BRCA2 (B2)-mutation carriers associated with an increased risk of breast cancer. J Clin Oncol 29: 2011 (suppl; abstr 1501). 2011 ASCO Annual Meeting.
29. Phillips KA, Milne RL, Rookus MA, Daly MB, Antoniou AC, Peock S, et al. Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2013;31(25):3091–9. https://doi.org/10.1200/JCO.2012.47.8313.
30. Peshkin BN, Isaacs C (2017). Overview of hereditary breast and ovarian cancer syndromes. In T. W. Post (Ed.), *UpToDate*. Retrieved from http://www.uptodate.com.
31. Liu KH, Skates S, Hernandez MA, Bedi D, Bevers T, Leeds L, et al. A 2-stage ovarian cancer screening strategy using the Risk of Ovarian Cancer Algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. Cancer. 2013;119(19):3454–61. https://doi.org/10.1002/cncr.28183.
32. Finch AP, Lubinski J, Moller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32(15):1547–53. https://doi.org/10.1200/JCO.2013.53.2820.
33. Segev Y, Iqbal J, Lubinski, Gronwald J, Lynch HT, Moller PJ, et al. The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations: an international prospective cohort study. Gynecol Oncol. 2013;130(1):127–31. https://doi.org/10.1016/j.ygyno.2013.03.027.
34. Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, Levine DA, et al. Uterine Cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. JAMA Oncol. 2016;2(11):1434–40. https://doi.org/10.1001/jamaoncol.2016.1820.
35. Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013;31(33):4188–98. https://doi.org/10.1200/JCO.2013.48.9021.
36. Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer. 2010;46(12):2275–84. https://doi.org/10.1016/j.ejca.2010.04.018.
37. Schrijver LH, Olsson H, Antonis A, Milne R, Phillips K, Andrieu N, et al. Oral contraceptive use and breast cancer risk: a cohort study of BRCA1 and mutation carriers [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1–5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017:77(13 Suppl):Abstract nr 4276, Abstract 4276: Oral contraceptive use and breast cancer risk: a cohort study ofBRCA1andBRCA2mutation carriers.
38. Micropoulos C, Selkirk CGH, Saya S, Bancroft E, Vertosick E, Dadaev T, et al. Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition. Br J Cancer. 2018;118(2):266–76. https://doi.org/10.1038/bjc.2017.429.
39. Evans DG (2017). Li-fraumeni syndrome. In T. W. Post (Ed.), *UpToDate*. Retrieved from http://www.uptodate.com
40. Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, et al. Associations between cancer predisposition testing panel genes and breast Cancer. JAMA Oncol. 2017;3(9):1190–6. https://doi.org/10.1001/jamaoncol.2017.0424.
41. Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 2003;63(20):6643–50.
42. Wilson JR, Bateman AC, Hanson H, An Q, Evans G, Rahman N, et al. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. J Med Genet. 2010;47(11):771–4. https://doi.org/10.1136/jmg.2010.078113.
43. Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res. 1994;54(5):1298–304.
44. Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, et al. Biochemical and imaging surveillance in germline TP53

mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 2016;17(9):1295–305. https://doi.org/10.1016/S1470-2045(16)30249-2.

45. Ballinger ML, Best A, Mai PL, Khincha PP, Loud JT, Peters JA, et al. Baseline surveillance in li-Fraumeni syndrome using whole-body magnetic resonance imaging: a meta-analysis. JAMA Oncol. 2017;3(12):1634–9. https://doi.org/10.1001/jamaoncol.2017.1968.
46. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst. 2013;105(21):1607–16. https://doi.org/10.1093/jnci/djt277.
47. Ngeow J, Sesock K, Eng C. Breast Cancer risk and clinical implications for germline PTEN mutation carriers. Breast Cancer Res Treat. 2017;165(1):1–8. https://doi.org/10.1007/s10549-015-3665-z.
48. Ngeow J, Stanuch K, Mester JL, Barnholtz-Sloan JS, Eng C. Second malignant neoplasms in patients with Cowden syndrome with underlying germline PTEN mutations. J Clin Oncol. 2014;32(17):1818–24. https://doi.org/10.1200/JCO.2013.53.6656.
49. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7. https://doi.org/10.1158/1078-0432.CCR-11-2283.
50. Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet. 2013;50(4):255–63. https://doi.org/10.1136/jmedgenet-2012-101339.
51. Nieuwenhuis MH, Kets CM, Murphy-Ryan M, Yntema HG, Evans DG, Colas C. Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. Familial Cancer. 2014;13(1):57–63. https://doi.org/10.1007/s10689-013-9674-3.
52. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209–15.
53. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colorectal Cancer Screening Version 2.2017. NCCN.org.
54. Pharoah PD, Guilford P, Caldas C. International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121(6):1348–53.
55. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Gastric Cancer Version 5.2017. NCCN.org.
56. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497–506. https://doi.org/10.1056/NEJMoa1400382.a.