**Name of journal: *World Journal of Obstetrics and Gynecology***

**ESPS Manuscript NO: 21073**

**Manuscript Type: Minireviews**

**Implications of multigene testing for hereditary breast cancer in primary care**

Trivedi MS *et al*. Multigene testing for hereditary breast cancer

**Meghna S Trivedi, Katherine D Crew**

**Meghna S Trivedi,** Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY 10032, United States

**Katherine D Crew,** Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032, United States

**Katherine D Crew,** Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY 10032, United States

**Katherine D Crew,** Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY 10032, United States

**Author contributions:** Trivedi MS and Crew KD contributed equally to this work.

**Conflict-of-interest** **statement:** There is no conflict of interest associated with any of the authors who contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Katherine D Crew, MD, MS, Assistant Professor** of Medicine and Epidemiology, Herbert Irving Comprehensive Cancer Center, Columbia University, 161 Fort Washington Ave, 10-1072, New York, NY 10032, United States. kd59@cumc.columbia.edu

**Telephone:** +1-212-3051732

**Fax:** +1-212-3050178

**Received:** June 28, 2015

**Peer-review started:** July 11, 2015

**First decision:** October 8, 2015

**Revised:** October 29, 2015

**Accepted:** January 5, 2016

**Article in press:**

**Published online:**

**Abstract**

Approximately 1 in 8 women will develop breast cancer during their lifetime and the risk factors include age, family history, and reproductive factors. In women with a family history of breast cancer, there is a proportion in which a gene mutation can be the cause of the predisposition for breast cancer. A careful assessment of family and clinical history should be performed in these women in order to determine if a genetic counseling referral is indicated. In cases of hereditary breast cancer, genetic testing with a multigene panel can identify specific genetic mutations in over 100 genes. The most common genes mutated in hereditary breast cancer are the high-penetrance *BRCA1* and *BRCA2* genes. In addition, other mutations in high-penetrance genes in familial cancer syndromes and mutations in DNA repair genes can cause hereditary breast cancer. Mutations in low-penetrance genes and variants of uncertain significance may play a role in breast cancer development, but the magnitude and scope of risk in these cases remain unclear, thus the clinical utility of testing for these mutations is uncertain. In women with high-penetrance genetic mutations or lifetime risk of breast cancer > 20%, risk-reducing interventions, such as intensive screening, surgery, and chemoprevention, can decrease the incidence and mortality of breast cancer.

**Key words:** Genetic testing; *BRCA1*; *BRCA2*; Hereditary breast cancer; Multigene testing

© **The Author(s) 2016**. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Multigene testing for hereditary breast cancer is readily available and some panels can identify over 100 gene mutations. Risk-reducing strategies are available for women with mutations in high-penetrance genes, whereas strategies for managing women with mutations in low-moderate penetrance genes is less clear. Appropriately identifying women who should undergo genetic counseling for hereditary breast cancer and implementing recommended guidelines in those who are found to be high risk can reduce the incidence and mortality of breast cancer.

Trivedi MS, Crew KD. Implications of multigene testing for hereditary breast cancer in primary care. *World J Obstet Gynecol* 2016; In press

**INTRODUCTION**

Approximately 1 in 8 women will develop breast cancer during their lifetime[1]. There are many risk factors for the development of breast cancer, including increasing age, reproductive factors, and family history of breast cancer. Thirteen percent of women diagnosed with breast cancer have at least one first-degree relative with breast cancer and the risk of developing breast cancer increases with increasing numbers of affected first-degree relatives when compared to women with no affected relatives[2]. A proportion of these women develop breast cancer due to inheriting a mutated gene. This is classified as a hereditary breast cancer. Hereditary breast and ovarian cancer (HBOC) syndrome is secondary to mutations in the *BRCA1* and *BRCA2* genes and accounts for 20%-25% of breast and ovarian cancers in families with multiple affected family members[3,4]. There are several other defined syndromes associated with hereditary breast cancer, including Cowden (*PTEN* mutation), Li-Fraumeni (*TP53* mutation), Peutz-Jeghers (*STK11* mutation), and hereditary diffuse gastric cancer (*CDH1* mutations) syndromes[5]. Additionally, there are other low and moderate penetrance genes, including *PALB2*, *CHEK2*, and *ATM*, that can cause clustering of breast cancer in affected families.

Genetic testing for these gene mutations can allow for identification of these patients prior to the development of cancer. In the case of some mutations, there are interventions that can reduce breast cancer incidence and mortality in mutation carriers. Recent advances in technology allow for rapid and low cost identification of inherited mutations. While individuals can be tested for only *BRCA1/2* mutations specifically, there is also multigene testing that utilizes next generation sequencing (NGS), which can identify mutations in over 100 genes in one test[6]. Though multigene testing is readily available in the clinics and through direct-to-consumer testing[7], the clinical utility of evaluating the large number of genes remains uncertain.

This review article will summarize the indications for genetic assessment for hereditary breast cancer, the evidence on interpretation of multigene testing results, and breast cancer risk management options for women who are found to be carriers of mutations.

**INDICATIONS FOR GENETIC ASSESSMENT IN HEREDITARY BREAST CANCER**

Several professional organizations, including the National Comprehensive Cancer Network (NCCN)[8], the United States Preventive Services Task Force (USPSTF)[9], the American Society of Clinical Oncology (ASCO)[7,10], the National Society of Genetic Counselors (NSGC)[5,11], the American College of Medical Genetics (ACMG)[11], and the American College of Obstetricians and Gynecologists (ACOG)[12] have published guidelines regarding genetic assessment for hereditary breast cancer in cancer-free women. As part of a genetic assessment, these guidelines all emphasize the importance of genetic counseling prior to and after genetic testing by a health care provider knowledgeable in genetic testing. While the specific criteria for referral to genetic assessment vary among different organizations, the criteria are based on the clinical features and history that increase the likelihood of a hereditary breast cancer. Table 1 shows the guidelines for hereditary breast cancer genetic assessment in a woman without a cancer diagnosis as published by the NCCN, USPSTF, ASCO, NSGC, ACMG, and ACOG.

There are also specific guidelines for genetic assessment in patients who have received a diagnosis of cancer and also for men; however, these guidelines will not be discussed in this review.

**MULTIGENE TESTING FOR HEREDITARY BREAST CANCER**

There are several commercially available multigene panels for hereditary breast cancer, such as BreastNext by Ambry Genetics, OncoGeneDx by GeneDx, and myRisk by Myriad Genetics, that are capable of sequencing a range of 6 to more than 100 cancer-associated genes depending on the test[6,13]. The specific genes tested in each multigene panel vary depending on the laboratory offering the testing. Some of the genes included in these panels are genes that are known to be associated with cancer syndromes with breast cancer component (*i.e.*, *BRCA1/2* for hereditary breast and ovarian cancer syndrome, *PTEN* for Cowden syndrome, *TP53* for Li-Fraumeni syndrome), genes shown to have a moderate risk association with breast cancer, or genes that function in DNA repair pathways with or similarly to *BRCA1/2*. However, there are concerns that other genes included in multigene panels have breast cancer risk associations that are not well established[6,13,14]. This complicates the testing of these less-established genes on three levels of uncertainty: the magnitude of cancer risk associated with the gene, the clinical scope of cancer risk, and the clinical relevance of variants of the genes[13].

Additionally, NGS has the potential to discover variants of uncertain significance (VUS) at high rates[15]. In a study of 198 women who met NCCN guidelines for *BRCA1/2* mutation testing, multigene testing with a panel of 42 genes was performed and participants were found to have an average of 2.1 VUS among 42 genes[16]. The high rate of VUS poses a risk of causing unnecessary anxiety and potentially interventions that are without evidence base[13].

In families that do not have *BRCA1* or *BRCA2* mutations, it is likely that other high-penetrance genes or a number of moderate- or low-penetrant genes account for familial breast cancer[3]. In a study in the United States, among women who met NCCN guidelines for *BRCA1/2* testing and had negative genetic testing, 11.4% had pathogenic mutations in one of 40 other genes[16]. A study in Germany performed multigene testing with a panel of 10 genes on 620 patients who met criteria for HBOC genetic testing and found almost 33% more mutations could be discovered with the addition of 8 genes to *BRCA1* and *BRCA2* testing[17]. The use of multigene testing could help identify mutations that may cause the predisposition to breast cancer of the approximately 75%-80% of familial breast cancers that are not associated with *BRCA1/2* mutations.

While mutations in genes that have a well-established risk association with breast cancer, such as *BRCA1/2*, have clear clinical implications, there is uncertainty with how to interpret and communicate the results of mutations in genes with less robust evidence, as well as gene variants of uncertain significance. Genes that have evidence of an association with breast cancer are described below.

***BRCA1/BRCA2 (hereditary breast and ovarian cancer syndrome)***

*BRCA1/2* genes play a role in DNA repair and mutations in these genes are of high-penetrance. Women with a *BRCA1/2* mutation have elevated lifetime risks of breast and ovarian cancer of 40%-60% and 20%-40%, respectively[18-21]. There is also an increased risk of other cancers, such as pancreas cancer. While the prevalence of the genetic mutation is less than 1% (1 in 400) in the general population, the prevalence of a founder mutation in the *BRCA1* (5382insC or 185delAG) or *BRCA2* (6174delT) genes is up to 2.5% (1 in 40) among individuals of Ashkenazi (Central and Eastern European) Jewish descent[21,22]. There are over 2000 different known mutations in the *BRCA1/2* genes[23]. There is also evidence to suggest that there are genetic modifiers of breast cancer risk for carriers of *BRCA* mutations and that the type and location of *BRCA* mutation affects breast cancer risk[24,25]. Genetic test results are reported as positive, VUS, uninformative-negative, or true negative[9]. The difference between uninformative-negative and true negative is that a true negative result is when no *BRCA* mutation is found in the setting of a known *BRCA* mutation in the family[26]. In a large cross-sectional study of non-Ashkenazi women who underwent *BRCA* mutation testing, 6.2% were found to have VUS. Populations that are genetically distinct and/or under-tested, such as racial/ethnic minorities, will have higher rates of VUS when compared to the white/European reference population; however, with increased volume of testing and reclassification of VUS, the rates of VUS reporting have declined over time[27].

***Genes responsible for tumor syndromes***

There are several well characterized high-penetrance hereditary tumor syndromes in which breast cancer is one manifestation of the syndrome. While the association of these syndromes with an increase in breast cancer risk is known, the exact increase in risk is difficult to estimate due to ascertainment bias[6]. Li-Fraumeni syndrome is a due to a germline mutation in the *TP53* gene, a tumor suppressor gene, and is characterized by an increased risk for childhood sarcomas, brain tumors, adrenocortical carcinoma, childhood leukemia, and other cancers, in addition to breast cancer[28]. In a study assessing the cancer incidence in 56 *TP53* germline mutation carriers and 3201 non-carriers, there was a significantly higher risk of breast cancer in female *TP53* mutation carriers, with a standardized incidence ratio of 105.1 (95%CI, 55.9-179.8)[29]. Cowden syndrome, or multiple hamartoma syndrome, is due to a germline mutation in the *PTEN* gene, a tumor suppressor gene[30]. The clinical phenotype has a wide array of abnormalities, including behavioral disorders, macrocephaly, gastrointestinal hamartomas, thyroid cancer, and endometrial cancer, in addition to breast cancer[31]. The estimated lifetime risk of breast cancer in a female *PTEN* mutation carrier is 85.2%, with a standardized incidence ratio of breast cancer of 25.4 (95%CI, 19.8-32.0)[32]. Germline mutations in the *STK11* gene, another tumor suppressor gene, cause Peutz-Jeghers syndrome. This syndrome is characterized by mucocutaneous pigmentation and gastrointestinal polyposis as well as an increase in gastrointestinal, breast, ovary, uterus, lung, and testis cancers[33]. The risk of developing breast cancer in a female *STK11* mutation carrier is 45% by age 70 years, a 6-fold increase when compared to the general population[33]. Hereditary diffuse gastric cancer is due to a germline mutation in the *CDH1* gene, which encodes for the E-cadherin protein. This mutation results in an increased risk of diffuse gastric cancer, colorectal cancer, and breast cancer, specifically lobular breast cancer. In female mutation carriers, the cumulative risk of breast cancer by age 80 is 39%, with a relative risk of developing breast cancer of 6.6 when compared to the general population[34]. Finally, neurofibromatosis type 1 (NF1) is caused by a germline mutation in the *NF1* gene, which encodes for neurofibromin, and is also a tumor suppressor gene. This syndrome has a phenotype of dermatologic manifestations, vascular disease, bone deformities, cognitive difficulties, and an increased risk of neoplasms, including breast cancer[35]. Cohort studies have shown a higher than expected number of breast cancer cases in women with NF1 with an estimated relative risk of 2.6 (90%CI, 2.1-3.2)[6,35,36].

***Genes involved in DNA repair***

Mutations in other genes that are involved in DNA repair, such as *PALB2, CHEK2, ATM,* and *NBN*, have also been shown to be associated with an increased risk of breast cancer and are characterized as moderate-penetrance variants. The *PALB2* gene encodes a protein that interacts with both *BRCA1* and *BRCA2* in DNA repair[37]. Several studies have shown that mutations in *PALB2* are associated with increased risk of breast cancer[38-41]. A meta-analysis found the combined relative risk to be 5.2 (90%CI, 3.0-9.4) [6]. The *CHEK2* gene encodes a kinase that responds to DNA damage. In 2 large case-control studies, a specific variant of *CHEK2*, c.1100delC, was found to increase the risk of breast cancer by an estimated relative risk of 3.0 (90%CI, 2.6-3.5)[6,42,43]. The *ATM* gene encodes a protein kinase that functions in monitoring and repairing double-strand DNA breaks. The disease ataxia-telangiectasia is caused by biallelic mutations in the *ATM* gene. A case-control study of 964 patients found that the relative risk of breast cancer associated with *ATM* mutation is 2.37 (95%CI, 1.51-3.78)[44]. The *NBN* gene encodes a protein that, like *BRCA1* and *BRCA2*, plays a role in the homologous recombination repair pathway. In a meta-analysis of 10 case-control studies on the association of *NBN* 657del5 variants and breast cancer risk, which included 25365 subjects, the pooled odds ratio was found to be 2.66 (95%CI, 1.82-3.90)[45].

**INTERVENTIONS FOR HIGH RISK PATIENTS**

***BRCA mutation carriers***

Risk management options for women found to have *BRCA1/2* mutations have been well studied and the NCCN has published expert-opinion based guidelines for the management of these patients. The risk management options for mutation carriers include intensive breast cancer screening with clinical breast exam, mammography, and breast magnetic resonance imaging (MRI), risk-reducing surgeries such as prophylactic mastectomy and bilateral salpingo-oophorectomy, and chemoprevention.

NCCN guidelines recommend clinical breast exam every 6-12 mo starting at age 25 years, annual breast MRI or mammogram (if MRI unavailable) from age 25-29 years, and annual breast MRI and mammogram from age 30-75 years[8]. Screening with MRI should begin earlier than 25 years if there is family history of a breast cancer diagnosis prior to age 25 years[8]. In a meta-analysis of 11 prospective studies that screened women at high risk for breast cancer with mammography and MRI, the sensitivity of MRI was greater than mammography (77% *vs* 39%), but specificity of mammography greater than MRI (94.7% *vs* 86.3%). When mammography was combined with MRI, sensitivity was 94% and specificity was 77.2%[46]. In *BRCA1/2* mutation carriers, annual surveillance with MRI is associated with a significant reduction in advanced-stage breast cancer[47].

With regards to risk reducing surgery, NCCN guidelines recommend counseling *BRCA* mutation carriers on risk-reducing mastectomy (RRM) and risk-reducing salpingo-oopherectomy (RRSO)[8]. In a prospective cohort study of 1619 *BRCA1/2* mutation carriers, of the 247 women who underwent RRM, none developed breast cancer, while there were 98 cases of breast cancer in the 1372 women who did not have surgery[48]. NCCN guidelines recommend RRSO between the ages of 35-40 and upon completion of childbearing[8]. RRSO resulted in 72%-86% reduction in risk of ovarian cancer, 37% reduction in risk of breast cancer in *BRCA1* carriers, and a 64% reduction in risk of breast cancer in *BRCA2* carriers[48]. Mutation carriers who underwent RRSO compared to those who did not had a 79% reduction in ovarian cancer-specific mortality, 56% reduction in breast cancer-specific mortality[48], and a 60%-77% reduction in all-cause mortality[48,49].

The use of tamoxifen, raloxifene, and aromatase inhibitors have been studied as chemoprevention in women at high risk for breast cancer, though data in *BRCA1/2* mutation carriers is limited. The breast cancer prevention trial was a randomized placebo-controlled trial investigating whether tamoxifen reduces the incidence of breast cancer in high-risk women and found a 49% reduction in the incidence of breast cancer with the use of tamoxifen[50,51]. Of the 288 breast cancer cases in the trial, 19 were *BRCA* mutation carriers. Analysis showed that tamoxifen reduced breast cancer incidence among *BRCA2* carriers by 62%, but had no effect on breast cancer incidence in *BRCA1* carriers[52].

***Negative BRCA1/2 testing***

Despite negative *BRCA1/2* testing, families with a significant family history of breast cancer still have an approximately four-fold increased risk of breast cancer[26]. In these women, there are still interventions available that can decrease the risk of developing breast cancer. In women with a greater that 20% lifetime risk of breast cancer, either as calculated by a risk model or due to the presence of a high- or moderate-penetrance mutation (*i.e.,* *ATM*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11*, or *TP53*), NCCN guidelines recommend intensive screening with MRI[8]. Additionally, for women with *CDH1, PTEN,* or *TP53* mutations, option of RRM should also be discussed[8].

In women who have a 5-year breast cancer risk ≥ 1.67% or lifetime breast cancer risk ≥ 20%, chemoprevention is also an option. There is evidence that in this high risk population, tamoxifen, raloxifene, and aromatase inhibitors can decrease the incidence of breast cancer by approximately 50%, 40%, and 65%, respectively[51,53-55].

**CONCLUSION**

Women with a family history of breast or ovarian cancer should be screened for referral to genetic assessment for hereditary breast cancer. Advances in NGS have made multigene testing for hereditary breast cancer readily available; however, there remain questions about the clinical utility of such testing. For high- and moderate-penetrance mutations, there is greater clinical utility as there are established guidelines on risk management interventions that can be performed to reduce incidence and mortality from breast cancer.

**REFERENCES**

1 **Howlader N**, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER Cancer Statistics Review (CSR) 1975-2012. Bethesda, MD: National Cancer Institute. Available from: URL: http: //seer.cancer.gov/csr/1975\_2012/

2 [**Collaborative Group on Hormonal Factors in Breast Cancer**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Collaborative%20Group%20on%20Hormonal%20Factors%20in%20Breast%20Cancer%5BCorporate%20Author%5D). Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* 2001; **358**: 1389-1399 [PMID: 11705483 DOI: 10.1016/S0140-6736(01)06524-2]

3 **Antoniou AC**, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ, Easton DF. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer* 2002; **86**: 76-83 [PMID: 11857015 DOI: 10.1038/sj.bjc.6600008]

4 **Shih HA**, Couch FJ, Nathanson KL, Blackwood MA, Rebbeck TR, Armstrong KA, Calzone K, Stopfer J, Seal S, Stratton MR, Weber BL. BRCA1 and BRCA2 mutation frequency in women evaluated in a breast cancer risk evaluation clinic. *J Clin Oncol* 2002; **20**: 994-999 [PMID: 11844822 DOI: 10.1200/JCO.20.4.994]

5 **Berliner JL**, Fay AM, Cummings SA, Burnett B, Tillmanns T. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. *J Genet Couns* 2013; **22**: 155-163 [PMID: 23188549 DOI: 10.1007/s10897-012-9547-1]

6 **Easton DF**, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, Devilee P, Meindl A, Couch FJ, Southey M, Goldgar DE, Evans DG, Chenevix-Trench G, Rahman N, Robson M, Domchek SM, Foulkes WD. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med* 2015; **372**: 2243-2257 [PMID: 26014596 DOI: 10.1056/NEJMsr1501341]

7 **Robson ME**, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol* 2010; **28**: 893-901 [PMID: 20065170 DOI: 10.1200/JCO.2009.27.0660]

8 **National Comprehensive Cancer Network**. Genetic/familial high-risk assessment: Breast and ovarian. Version 2. 2015. http://www.nccn.org/professionals/physician\_gls/pdf/genetics\_screening.pdf

9 **Moyer VA**. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; **160**: 271-281 [PMID: 24366376 DOI: 10.7326/M13-2747]

10 [**American Society of Clinical Oncology**](http://www.ncbi.nlm.nih.gov/pubmed/?term=American%20Society%20of%20Clinical%20Oncology%5BCorporate%20Author%5D). American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003; **21**: 2397-2406 [PMID: 12692171 DOI: 10.1200/JCO.2003.03.189]

11 **Hampel H**, Bennett RL, Buchanan A, Pearlman R, Wiesner GL. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med* 2015; **17**: 70-87 [PMID: 25394175 DOI: 10.1038/gim.2014.147]

12 [**American College of Obstetricians and Gynecologists**](http://www.ncbi.nlm.nih.gov/pubmed/?term=American%20College%20of%20Obstetricians%20and%20Gynecologists%5BCorporate%20Author%5D); [ACOG Committee on Practice Bulletins--Gynecology](http://www.ncbi.nlm.nih.gov/pubmed/?term=ACOG%20Committee%20on%20Practice%20Bulletins--Gynecology%5BCorporate%20Author%5D); [ACOG Committee on Genetics](http://www.ncbi.nlm.nih.gov/pubmed/?term=ACOG%20Committee%20on%20Genetics%5BCorporate%20Author%5D); [Society of Gynecologic Oncologists](http://www.ncbi.nlm.nih.gov/pubmed/?term=Society%20of%20Gynecologic%20Oncologists%5BCorporate%20Author%5D). ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009; **113**: 957-966 [PMID: 19305347 DOI: 10.1097/AOG.0b013e3181a106d4]

13 **Kurian AW**, Kingham KE, Ford JM. Next-generation sequencing for hereditary breast and gynecologic cancer risk assessment. *Curr Opin Obstet Gynecol* 2015; **27**: 23-33 [PMID: 25502425 DOI: 10.1097/GCO.0000000000000141]

14 **Domchek SM**, Bradbury A, Garber JE, Offit K, Robson ME. Multiplex genetic testing for cancer susceptibility: out on the high wire without a net? *J Clin Oncol* 2013; **31**: 1267-1270 [PMID: 23460708 DOI: 10.1200/JCO.2012.46.9403]

15 **Walsh T**, Lee MK, Casadei S, Thornton AM, Stray SM, Pennil C, Nord AS, Mandell JB, Swisher EM, King MC. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci USA* 2010; **107**: 12629-12633 [PMID: 20616022 DOI: 10.1073/pnas.1007983107]

16 **Kurian AW**, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, McGuire V, Ladabaum U, Kobayashi Y, Lincoln SE, Cargill M, Ford JM. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014; **32**: 2001-2009 [PMID: 24733792 DOI: 10.1200/JCO.2013.53.6607]

17 **Schroeder C**, Faust U, Sturm M, Hackmann K, Grundmann K, Harmuth F, Bosse K, Kehrer M, Benkert T, Klink B, Mackenroth L, Betcheva-Krajcir E, Wimberger P, Kast K, Heilig M, Nguyen HP, Riess O, Schröck E, Bauer P, Rump A. HBOC multi-gene panel testing: comparison of two sequencing centers. *Breast Cancer Res Treat* 2015; **152**: 129-136 [PMID: 26022348 DOI: 10.1007/s10549-015-3429-9]

18 **Antoniou AC**, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. *J Med Genet* 2005; **42**: 602-603 [PMID: 15994883 DOI: 10.1136/jmg.2004.024133]

19 **Chen S**, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 2007; **25**: 1329-1333 [PMID: 17416853 DOI: 10.1200/JCO.2006.09.1066]

20 **King MC**, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003; **302**: 643-646 [PMID: 14576434 DOI: 10.1126/science.1088759]

21 **Struewing JP**, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997; **336**: 1401-1408 [PMID: 9145676 DOI: 10.1056/NEJM199705153362001]

22 **Roa BB**, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996; **14**: 185-187 [PMID: 8841191 DOI: 10.1038/ng1096-185]

23 **Christinat A**, Pagani O. Practical aspects of genetic counseling in breast cancer: lights and shadows. *Breast* 2013; **22**: 375-382 [PMID: 23673076 DOI: 10.1016/j.breast.2013.04.006]

24 **Milne RL**, Antoniou AC. Genetic modifiers of cancer risk for BRCA1 and BRCA2 mutation carriers. *Ann Oncol* 2011; **22** Suppl 1: i11-i17 [PMID: 21285145 DOI: 10.1093/annonc/mdq660]

25  **Rebbeck TR**, Mitra N, Wan F, Sinilnikova OM, Healey S, McGuffog L, Mazoyer S, Chenevix-Trench G, Easton DF, Antoniou AC, Nathanson KL, 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 EJ, 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 AH, 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**: 1347-1361 [PMID: 25849179 DOI: 10.1001/jama.2014.5985]

26 **Metcalfe KA**, Finch A, Poll A, Horsman D, Kim-Sing C, Scott J, Royer R, Sun P, Narod SA. Breast cancer risks in women with a family history of breast or ovarian cancer who have tested negative for a BRCA1 or BRCA2 mutation. *Br J Cancer* 2009; **100**: 421-425 [PMID: 19088722 DOI: 10.1038/sj.bjc.6604830]

27 **Hall MJ**, Reid JE, Burbidge LA, Pruss D, Deffenbaugh AM, Frye C, Wenstrup RJ, Ward BE, Scholl TA, Noll WW. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer* 2009; **115**: 2222-2233 [PMID: 19241424 DOI: 10.1002/cncr.24200]

28 **Malkin D**, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 1990; **250**: 1233-1238 [PMID: 1978757 DOI: 10.1126/science.1978757]

29 **Hwang SJ**, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. *Am J Hum Genet* 2003; **72**: 975-983 [PMID: 12610779 DOI: 10.1086/374567]

30 **Nelen MR**, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, Coulon V, Goldstein AM, van Reen MM, Easton DF, Eeles RA, Hodgsen S, Mulvihill JJ, Murday VA, Tucker MA, Mariman EC, Starink TM, Ponder BA, Ropers HH, Kremer H, Longy M, Eng C. Localization of the gene for Cowden disease to chromosome 10q22-23. *Nat Genet* 1996; **13**: 114-116 [PMID: 8673088 DOI: 10.1038/ng0596-114]

31 **Daly MB**, Pilarski R, Axilbund JE, Buys SS, Crawford B, Friedman S, Garber JE, Horton C, Kaklamani V, Klein C, Kohlmann W, Kurian A, Litton J, Madlensky L, Marcom PK, Merajver SD, Offit K, Pal T, Pasche B, Reiser G, Shannon KM, Swisher E, Voian NC, Weitzel JN, Whelan A, Wiesner GL, Dwyer MA, Kumar R. Genetic/familial high-risk assessment: breast and ovarian, version 1.2014. *J Natl Compr Canc Netw* 2014; **12**: 1326-1338 [PMID: 25190698]

32 **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**: 400-407 [PMID: 22252256 DOI: 10.1158/1078-0432.CCR-11-2283]

33 **Hearle N**, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, Keller JJ, Westerman AM, Scott RJ, Lim W, Trimbath JD, Giardiello FM, Gruber SB, Offerhaus GJ, de Rooij FW, Wilson JH, Hansmann A, Möslein G, Royer-Pokora B, Vogel T, Phillips RK, Spigelman AD, Houlston RS. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 2006; **12**: 3209-3215 [PMID: 16707622 DOI: 10.1158/1078-0432.CCR-06-0083]

34 **Pharoah PD**, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology* 2001; **121**: 1348-1353 [PMID: 11729114 DOI: 10.1053/gast.2001.29611]

35 **Madanikia SA**, Bergner A, Ye X, Blakeley JO. Increased risk of breast cancer in women with NF1. *Am J Med Genet A* 2012; **158A**: 3056-3060 [PMID: 23165953 DOI: 10.1002/ajmg.a.35550]

36 **Seminog OO**, Goldacre MJ. Age-specific risk of breast cancer in women with neurofibromatosis type 1. *Br J Cancer* 2015; **112**: 1546-1548 [PMID: 25742481 DOI: 10.1038/bjc.2015.78]

37 **Zhang F**, Ma J, Wu J, Ye L, Cai H, Xia B, Yu X. PALB2 links BRCA1 and BRCA2 in the DNA-damage response. *Curr Biol* 2009; **19**: 524-529 [PMID: 19268590 DOI: 10.1016/j.cub.2009.02.018]

38 **Erkko H**, Xia B, Nikkilä J, Schleutker J, Syrjäkoski K, Mannermaa A, Kallioniemi A, Pylkäs K, Karppinen SM, Rapakko K, Miron A, Sheng Q, Li G, Mattila H, Bell DW, Haber DA, Grip M, Reiman M, Jukkola-Vuorinen A, Mustonen A, Kere J, Aaltonen LA, Kosma VM, Kataja V, Soini Y, Drapkin RI, Livingston DM, Winqvist R. A recurrent mutation in PALB2 in Finnish cancer families. *Nature* 2007; **446**: 316-319 [PMID: 17287723 DOI: 10.1038/nature05609]

39 **Erkko H**, Dowty JG, Nikkilä J, Syrjäkoski K, Mannermaa A, Pylkäs K, Southey MC, Holli K, Kallioniemi A, Jukkola-Vuorinen A, Kataja V, Kosma VM, Xia B, Livingston DM, Winqvist R, Hopper JL. Penetrance analysis of the PALB2 c.1592delT founder mutation. *Clin Cancer Res* 2008; **14**: 4667-4671 [PMID: 18628482 DOI: 10.1158/1078-0432.CCR-08-0210]

40 **Antoniou AC**, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; **371**: 1651-1652 [PMID: 25337756 DOI: 10.1056/NEJMc1410673]

41 **Rahman N**, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, Reid S, Spanova K, Barfoot R, Chagtai T, Jayatilake H, McGuffog L, Hanks S, Evans DG, Eccles D, Easton DF, Stratton MR. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007; **39**: 165-167 [PMID: 17200668 DOI: 10.1038/ng1959]

42[**CHEK2 Breast Cancer Case-Control Consortium**](http://www.ncbi.nlm.nih.gov/pubmed/?term=CHEK2%20Breast%20Cancer%20Case-Control%20Consortium%5BCorporate%20Author%5D). 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**: 1175-1182 [PMID: 15122511 DOI: 10.1086/421251]

43 **Weischer M**, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, Van't Veer LJ, Garcia-Closas M, Hopper JL, Hall P, Andrulis IL, Devilee P, Fasching PA, Anton-Culver H, Lambrechts D, Hooning M, Cox A, Giles GG, Burwinkel B, Lindblom A, Couch FJ, Mannermaa A, Grenaker Alnæs G, John EM, Dörk T, Flyger H, Dunning AM, Wang Q, Muranen TA, van Hien R, Figueroa J, Southey MC, Czene K, Knight JA, Tollenaar RA, Beckmann MW, Ziogas A, Christiaens MR, Collée JM, Reed MW, Severi G, Marme F, Margolin S, Olson JE, Kosma VM, Kristensen VN, Miron A, Bogdanova N, Shah M, Blomqvist C, Broeks A, Sherman M, Phillips KA, Li J, Liu J, Glendon G, Seynaeve C, Ekici AB, Leunen K, Kriege M, Cross SS, Baglietto L, Sohn C, Wang X, Kataja V, Børresen-Dale AL, Meyer A, Easton DF, Schmidt MK, Bojesen SE. CHEK2\*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. *J Clin Oncol* 2012; **30**: 4308-4316 [PMID: 23109706 DOI: 10.1200/JCO.2012.42.7336]

44 **Renwick A**, Thompson D, Seal S, Kelly P, Chagtai T, Ahmed M, North B, Jayatilake H, Barfoot R, Spanova K, McGuffog L, Evans DG, Eccles D, Easton DF, Stratton MR, Rahman N. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. *Nat Genet* 2006; **38**: 873-875 [PMID: 16832357 DOI: 10.1038/ng1837]

45 **Zhang G**, Zeng Y, Liu Z, Wei W. Significant association between Nijmegen breakage syndrome 1 657del5 polymorphism and breast cancer risk. *Tumour Biol* 2013; **34**: 2753-2757 [PMID: 23765759 DOI: 10.1007/s13277-013-0830-z]

46 **Warner E**, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med* 2008; **148**: 671-679 [PMID: 18458280 DOI: 10.7326/0003-4819-148-9-200805060-00007]

47 **Warner E**, Hill K, Causer P, Plewes D, Jong R, Yaffe M, Foulkes WD, Ghadirian P, Lynch H, Couch F, Wong J, Wright F, Sun P, Narod SA. 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**: 1664-1669 [PMID: 21444874 DOI: 10.1200/JCO.2009.27.0835]

48 **Domchek SM**, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010; **304**: 967-975 [PMID: 20810374 DOI: 10.1001/jama.2010.1237]

49 **Finch AP**, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, Rosen B, Maehle L, Ghadirian P, Cybulski C, Huzarski T, Eisen A, Foulkes WD, Kim-Sing C, Ainsworth P, Tung N, Lynch HT, Neuhausen S, Metcalfe KA, Thompson I, Murphy J, Sun P, Narod SA. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. *J Clin Oncol* 2014; **32**: 1547-1553 [PMID: 24567435 DOI: 10.1200/jco.2013.53.2820]

50 **Fisher B**, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; **90**: 1371-1388 [PMID: 9747868 DOI: 10.1093/jnci/dji372]

51 **Fisher B**, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG, Runowicz CD, James JM, Ford LG, Wolmark N. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005; **97**: 1652-1662 [PMID: 16288118]

52 **King MC**, Wieand S, Hale K, Lee M, Walsh T, Owens K, Tait J, Ford L, Dunn BK, Costantino J, Wickerham L, Wolmark N, Fisher B. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001; **286**: 2251-2256 [PMID: 11710890 DOI: 10.1001/jama.286.18.2251]

53 **Vogel VG**, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER, Wade JL, Robidoux A, Margolese RG, James J, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer Prev Res* (Phila) 2010; **3**: 696-706 [PMID: 20404000 DOI: 10.1158/1940-6207.CAPR-10-0076]

54 **Goss PE**, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winquist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; **364**: 2381-2391 [PMID: 21639806 DOI: 10.1056/NEJMoa1103507]

55 **Cuzick J**, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G, Bonanni B, Palva T, Howell A. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2014; **383**: 1041-1048 [PMID: 24333009 DOI: 10.1016/S0140-6736(13)62292-8]

**P- Reviewer:** Cosmi E, Khajehei M, Sonoda K, Tsikouras P, Yokoyama Y

**S- Editor:** Gong XM

 **L- Editor:** **E- Editor:**

**Table 1 Guidelines for hereditary breast cancer genetic assessment in a woman without a cancer diagnosis**

|  |  |
| --- | --- |
| **Organization** | **Indications for genetic assessment referral** |
| **National Comprehensive Cancer Network[8]**  | **Family history of any of the following:**A known mutation in a cancer susceptibility gene within the family≥ 2 breast cancer primaries in a single individual≥ 2 individuals with breast cancer primaries on the same side of family≥ 1 individual with invasive ovarian cancer primaryFirst- or second-degree relative with breast cancer at age ≤ 45 yrThree or more of the following (especially if early onset): Pancreatic cancer, prostate cancer (Gleason score ≥ 7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal tract, diffuse gastric cancer (can include multiple primary cancers in same individual)Male breast cancer |
| **United States Preventive Services Task Force[9]** | **Family history of any of the following:**Breast cancer diagnosis before age 50 yrBilateral breast cancerBreast and ovarian cancerBreast cancer in ≥ 1 male family memberMultiple cases of breast cancer in the family≥ 1 family member with 2 primary types of BRCA-related cancerAshkenazi Jewish ethnicityOR use of a familial risk stratification tool, such as the Ontario Family History Assessment Tool, Manchester scoring system, Referral Screening Tool, Pedigree Assessment Tool, and Family History Screen 7, to determine need for genetic counseling |
| **American Society of Clinical Oncology[7,10]** | **When all 3 criteria are met:**The individual being tested has a personal or family history suggestive of genetic cancer susceptibilityThe genetic test can be adequately interpretedThe test results have accepted clinical utility |
| **National Society of Genetic Counselors[5,11] and American College of Medical Genetics and Genomics[11]** | **If patient or any of their first-degree relatives meet one of the following criteria:**Breast cancer diagnosis at age ≤ 50Triple-negative breast cancer diagnosis at age ≤ 60≥ 2 primary breast cancers in the same personAshkenazi Jewish ancestry and breast cancer at any age≥ 3 cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer in close relatives, including the patientBreast cancer and one additional Li-Fraumeni Syndrome tumor in the same person or in two relatives, one diagnosed at age ≤ 45 yrBreast cancer and ≥1 Peutz-Jeghers polyp in the same personLobular breast cancer and diffuse gastric cancer in the same personLobular breast cancer in one relative and diffuse gastric cancer in another, one diagnosed at age < 50Breast cancer and 2 additional Cowden syndrome criteria in the same person |
| **American College of Obstetricians and Gynecologists (ACOG)[12]** | **Women with greater than an approximate 20%-25% chance of having an inherited predisposition to breast and ovarian cancer are recommended for genetic counseling referral, including:**Women with a close relative with known *BRCA1* or *BRCA2* mutations**In women with greater than an approximate 5%-10% chance of having an inherited predisposition to breast and ovarian cancer, genetic counseling referral may be helpful, including those with a close relative that has:**Breast cancer at age ≤ 40 yrOvarian cancer, primary peritoneal cancer, or fallopian tube cancer of high grade, serous histology at any ageBilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age ≤ 50 yr)Breast cancer at age ≤ 50 yr and a close relative with breast cancer at age ≤ 50 yrAshkenazi Jewish ancestry with breast cancer at age ≤ 50 yrBreast cancer at any age and two or more close relatives with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age ≤ 50 yr) |