Breast Cancer Genetics and Risk Assessment

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Introduction

An accurate estimation of breast cancer risk is essential in guiding clinical management for women at all levels of risk. The goal of providing the appropriate clinical management is to increase survival in high-risk women and decrease cost and complications in low-risk women. Women can be at high risk of developing breast cancer based on benign disease (like ADH and LCIS) as well as family history of cancer. While the former is determined by the surgeon, the genetic counselor is essential in using the family history to distinguish those at high risk for breast cancer.

Recognizing Risk

It is essential to identify women who would benefit from genetic counseling and risk assessment and refer them to a provider who can assess risk using the aforementioned models and clinical judgment. Several health and professional organizations strongly encourage referral to a certified/credentialed cancer genetics professional for pretest counseling, prior to genetic testing. The National Comprehensive Cancer Network® (NCCN®) has established criteria for those individuals that need further genetics risk assessment (Box 1.1). If an individual meets these criteria, the NCCN® recommends that individual be referred to a cancer genetics professional for further work-up and potential genetic testing [1]. While these criteria are very helpful in identification, each individual practice/institution should establish a protocol so that the criteria are utilized.

The process of identifying and referring those needing further genetics assessment varies widely. Many practices will rely on physicians and other health-care providers to recognize and refer these individuals for further risk assessment [2]. The success of this strategy, however, relies on multiple factors – the strongest of which is patient inquiry about their need for genetic testing for cancer [3, 4]. Other programs implement a "pen and paper" family history questionnaire that is reviewed by a trained staff member to identify and refer for genetic counseling. Still others use a more complex approach, where a patient inputs his or her personal and family history into a computerized software program, and the software identifies those needing genetic counseling [5–7]. This software output must be reviewed systematically so as no woman identified as "high risk" is overlooked. The use of the Internet in the identification of at-risk women is a potentially powerful tool, and interest in this modality is high [8]. More research is needed to determine which of the strategies noted herewith are most efficient at identifying individuals at risk [9, 10].

Once an individual is recognized as being at increased risk, it is important that they are referred to a cancer genetics professional [1] as the importance of pretest and post-test genetic counseling for cancer susceptibility testing is widely recognized [11]. Referral to a cancer genetics professional is also important because the provider ordering the genetic testing must understand the complexities of genetic testing and the appropriate interpretation of the test results. One study reported that patients undergoing genetic testing for APC mutations often received inadequate counseling and would have been given incorrectly interpreted results [12]. The authors concluded that physicians should be prepared to offer

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M.K. Shetty (ed.), *Breast Cancer Screening and Diagnosis: A Synopsis*,
DOI 10.1007/978-1-4939-1267-4_1, © Springer Science+Business Media New York 2015

Box 1.1 NCCN Criteria for Referral to Genetics Provider: Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria [a,b,c] (V4.2013)

Individual from a family with a known deleterious BRCA1/BRCA2 mutation

Personal history of breast cancer[d] + one or more of the following:

- Diagnosed at age ≤45 years
- Two breast primaries[e] when first breast cancer diagnosis occurred ≤ age 50 years
- Diagnosed at age ≤50 years with ≥1 close blood relative with breast cancer at any age or with a limited family history
- Diagnosed at age ≤60 years with a triple-negative breast cancer
- Diagnosed at any age with ≥1 close blood relative[f] with breast cancer diagnosed ≤50 years
- Diagnosed at any age with ≥2 close blood relatives[f] with breast cancer at any age
- Diagnosed at any age with ≥1 close blood relative with epithelial ovarian cancer
- Diagnosed at any age with ≥2 close blood relatives[f] with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
- Close male blood relative[f] with breast cancer
- For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required.[g]

Personal history of epithelial ovarian[h] cancer

Personal history of male breast cancer

Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives[f] with breast and/or ovarian[h] and/or pancreatic or aggressive prostate cancer (Gleason score ≥7) at any age

Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):

- First- or second-degree blood relative meeting any of the above criteria
- Third-degree blood relative with breast cancer[d] and/or ovarian[h] cancer with ≥2 close blood relatives[f] with breast cancer (as least one with breast cancer ≤50 years) and/or ovarian[h] cancer
- Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of the female unaffected relatives who link the patient with the affected relatives
- Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing

HBOC testing criteria met, then see follow-up (HBOC-2)

HBOC testing criteria not met, then cancer screening as per NCCN screening guidelines

[a]One or more of these criteria are suggestive of hereditary breast/ovarian cancer syndrome that warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. The maternal and paternal sides should be considered independently. Melanoma has been reported in some HBOC families

[b]Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

[c]Individuals with limited family history, such as fewer than 2 first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation

[d]For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included

[e]Two breast primaries include bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously

[f]Close blood relatives include first-, second-, and third-degree relatives on the same side of family (see BR/OV-3)

[g]Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria are met. Founder mutations exist in other populations

[h]For the purposes of these guideline, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome/hereditary nonpolyposis colorectal cancer; be attentive for clinical evidence of this syndrome. See NCCN guidelines for colorectal cancer screening

genetic counseling if they order genetic tests. Another study examining the genetic testing ordered at a large genetic testing company (including genetic testing for hereditary predisposition to cancer) showed that as high as 30 % of all ordered tests were inappropriately ordered [13]. Among frequently misordered tests in this study were requests for full gene sequencing when a familial mutation was known or when a screening panel would have been more appropriate. These studies suggest that if a physician is not adequately trained in the complexities of cancer genetic testing, a referral to cancer genetics professional should be made. The genetics professional will obtain a more detailed family history and determine who is appropriate for genetic testing. Practice guidelines exist to guide the genetic counselor in this process [14, 15].

Defining Risk

There exist various models which are used to estimate a woman's risk of breast cancer (Table 1.1). Most of these models can be classified into two groups: those that estimate the risk of developing breast cancer over time [16, 17] and those that estimate the probability of detecting a mutation in a cancer susceptibility gene [18, 19]. The most commonly used breast cancer risk assessment models are the Gail and Claus models. The model of Gail and colleagues [16] estimates breast cancer risk by taking into account a woman's age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and previous biopsies, with specific focus on the presence of atypical hyperplasia. The Gail model will underestimate the risk of developing breast cancer in many women with a family history of cancer as it does not include breast cancer in non-first-degree relatives or a family history of ovarian cancer [20]. For this reason, the model is more appropriately used to determine breast cancer risk in individuals who do not have family histories suggestive of a hereditary breast cancer syndrome or who have tested negative for a known genetic mutation. The tables of Claus and colleagues [17] also determine the risk of breast cancer for unaffected women, taking into consideration the number and age at breast cancer diagnosis of first- and second-degree female

Table 1.1 Models used to predict the risk of breast cancer and the probability of a BRCA mutation

Model	Variables in model	Comments/limitations
Risk of breast cancer for unaffected women		
Gail et al. [16] Provides risk of breast cancer by a given age Available as an interactive tool at www.cancer.gov/bcrisktool	Age, FH of breast cancer, reproductive factors (age at menarche, menopause, and first childbirth and the number of live births), number of breast biopsies, personal history of atypia	Does not incorporate paternal FH of breast or ovarian cancer; does not include breast cancer in non-FDR; does not consider age of onset of breast cancer in relatives; derived from a population undergoing screening
Claus et al. [17] Provides 5-year and lifetime probability of breast cancer Available for download at www4.utsouthwestern.edu/breasthealth/cagene/default.asp	Age, FH of breast cancer (first- and second-degree relatives)	Limited to specific combinations of affected relatives; does not incorporate risk factors other than family history
Probability of detecting BRCA mutation (affected and unaffected women)		
Tyrer et al. [18] Also provides a 10-year and lifetime probability of breast cancer	Personal or family history of breast and ovarian cancer, Ashkenazi ethnic background	Incomplete validation, especially in nonwhite populations
Frank et al. [21] Provides empirical experience of one laboratory Available for download at www.myriadtests.com/provider/brca-mutation-prevalence.htm	Personal or family history of breast and ovarian cancer, Ashkenazi ethnic background	Empirical model with incomplete validation; does not include unaffected family members
BRCAPRO [19] Also provides age-specific probability of breast cancer Available for download at www4.utsouthwestern.edu/breasthealth/cagene/default.asp	Personal or family history of breast or ovarian cancer, Ashkenazi ethnic background	Requires information on all affected and unaffected family members; incorporates only FDR and SDR relatives and may need to change proband to best capture risk; uses high-penetrance estimates

Abbreviations: *FH* family history, *FDR* first-degree relative, *SDR* second-degree relative

relatives. Despite this, the Claus model also underestimates the risk of a woman developing breast cancer if she has a hereditary predisposition to developing breast cancer because it does not take into consideration ethnicity or the presence of ovarian cancer in the family. This model, too, is more helpful in women without a family history suggestive of a known hereditary cancer syndrome.

For women with a family history of cancer, there exist models that help determine the likelihood of indentifying a mutation in a highly penetrant cancer susceptibility gene. There are a handful of models that are designed to estimate the likelihood of identifying a mutation in the *BRCA1* or *BRCA2* gene [18, 19, 21–23], for example. These models have both strengths and limitations that health-care providers must be familiar with to use and interpret them appropriately [24–26]. Probably the most widely used model is BRCAPRO which estimates the probability that an individual is a carrier of a *BRCA* mutation using family history and Bayes' theorem [19]. One limitation of the model is that it only incorporates relevant family history up to the second-degree relatives, potentially underestimating the probability of *BRCA* mutations in individuals with extended family history (e.g., early-onset breast cancer or ovarian cancer in cousins). On the other hand, the BRCAPRO model analysis is based primarily on large, high-penetrance families, thus this may lead to overestimation of risk in a more diverse risk assessment clinic.

A web-based model to predict the likelihood of identifying a mutation in the PTEN gene (which is responsible for Cowden syndrome) has been proposed by the researchers at Cleveland Clinic (http://www.lerner.ccf.org/gmi/ccscore/documents/adult_criteria.php). This model is based on a paper by Tan and colleagues [27] and proposes a clinical scoring system for selection of patients for PTEN mutation on the basis of a prospective study of 3,042 probands. The web-based model consists of a series of >20 clinical questions, with the output result of >3 % being the threshold for consideration of PTEN genetic testing. The major limitation of this model is that there is probable referral bias in the data it was based on, as the data were derived from two cohorts of patients representing patients recruited at two major cancer centers. While not a risk assessment model, the NCCN also has proposed criteria for when to offer PTEN testing. In these criteria, many of the clinical correlates present in the PTEN risk assessment model proposed by the Cleveland Clinic are removed. It remains unclear which of the previously mentioned is the most appropriate for determining those individuals at risk for PTEN mutations.

There are no statistical models that predict the likelihood of identifying mutations in the *TP53* or *CDH1* genes to date. Because there is no well-defined risk assessment model, it is important to be able to recognize other genetic syndromes based on personal and family history. (Please refer to full discussion of individual syndromes later in this chapter.)

It is important when using any risk assessment model to understand the limitations of these risk calculations and to place risk estimates into the appropriate context. It is important to note that risk estimates calculated by different models may vary—a factor that complicates the use of quantitative thresholds for making screening recommendations [28]. The health-care provider must use clinical judgment in addition to the estimates from models in order to provide the most precise risk assessment for an individual patient.

Genetic Counseling

The genetics professional will most often begin the assessment with collecting a detailed 3- generation family history in the form of a pedigree [29, 30]. It is important to gather information on both maternal and paternal lineages, with particular focus on individuals with malignancies (affected). Table 1.2 illustrates effective questions used by providers in obtaining this information [31]. It is imperative to include those family members without a personal history of cancer (unaffected) because the ratio and pattern of affected and unaffected influences the risk assessment. It is equally important to include the presence of nonmalignant findings in the proband and family members, as some inherited cancer syndromes have other physical characteristics associated with them (e.g., trichilemmomas with Cowden syndrome).

Table 1.2 Useful questions to use when obtaining a family history

Questions to ask all patients	Questions to ask patients who have had cancer or regarding relatives with cancer
Age	Organ in which tumor developed
Personal history of benign or malignant tumors	Age at time of diagnosis
Major illnesses	Number of tumors[a]
Hospitalizations	Pathology, stage, and grade of malignant tumors
Surgeries	Pathology of benign tumors
Biopsy history	Treatment regimen (surgery, chemotherapy, radiation)
Reproductive history[b]	Age at time of diagnosis
Cancer surveillance	
Environmental exposures	

Data from Trepanier et al. [31]

[a]For patients who have developed more than one tumor, it is important to discriminate whether the additional tumor(s) was a separate primary, recurrence, or the result of metastatic disease

[b]Especially important for women at increased risk of breast, ovarian, or endometrial cancer. Inquire about age at menarche, age at first live birth, history of oral contraceptive use, infertility medications, or hormone replacement therapy including dosage and duration, and age at menopause

When taking the family history, the accuracy of the information obtained from an individual patient should be considered. Sometimes individuals are even unclear about their own medical health history. One study reported that individuals who have had colonic polyps identified on colonoscopy do not recall key details about their own polyps (number, size, or pathology features) required to establish appropriate screening and surveillance intervals [32].

When talking about relatives, many factors can influence an individual's knowledge of their family history. A recent study indicates that individuals are often confident that a family member has had cancer but are typically unsure of the details surrounding that diagnosis [9, 33]. Reports of breast cancer tend to be accurate, while reports of ovarian cancer are less trustworthy [34, 35]. In a large study of 2,605 relatives that were sampled for confirmation of cancer reports on breast, colorectal, prostate, and lung cancer, sensitivity and positive predictive values were low to moderate and varied by cancer type: 60.2 and 40.0 %, respectively, for lung cancer reports, 27.3 and 53.5 % for colorectal cancer reports, 61.1 and 61.3 % for breast cancer reports, and 32.0 and 53.4 % for prostate cancer reports [36]. Studies have also found significant reporting differences between maternal and paternal family history of cancer, in addition to degree of relative [36, 37]. It is also important to note that family histories can change over time, with new diagnoses arising in family members as time passes [38]. See Box 1.2 [39].

All of these factors must be considered during the consultation, as the risk assessment and differential diagnosis is based primarily on this information. The primary purpose of the risk assessment process is to distinguish a hereditary form of cancer from familial clustering of cancer and sporadic forms of cancer. Features of a family history that are suggestive of a hereditary cancer syndrome include a preponderance of relatives with similar or related cancers; earlier age at onset of cancer; autosomal dominant pattern of cancer inheritance; the presence of rare cancers; the presence of multifocal, bilateral, or multiple primary cancers in one individual; and the absence of environmental risk factors. When a hereditary form of cancer is suspected, genetic testing should be entertained.

Box 1.2 Challenges in Collecting an Accurate Family History

Family history is incomplete
Family members live far away
Clients are not prepared to answer questions
Cancer is not discussed in the family
Family history information is not available
Lost contact with relatives
Estrangement from the family
Adoption
Reported history is false
Mistaken about the cancer diagnosis
Confused about the diagnosis
Deliberately fabricating history

Adapted from Schneider [39]

Although some published guidelines for genetic testing exist, much of the time the decision to offer genetic testing is based on clinical judgment. The American Society of Clinical Oncology (ASCO) recommends that genetic testing be offered when (1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, (2) the test can be adequately interpreted, and (3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer [11]. The NCCN provides NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for individuals that should be offered genetic testing for hereditary breast/ovarian cancer syndrome, Li-Fraumeni syndrome, and Cowden syndrome [1]. In the end, however, it is up to the individual provider's judgment as to whether or not genetic testing is indicated.

Genetic Testing Process

Once it has been determined that genetic testing is appropriate, the next step is to determine which individual in the family should be tested first. If there is not a known mutation in a family, testing should begin with a person that has the highest probability of finding a mutation. Typically, this is a person who has been diagnosed with cancer at an early age. If there is no such person available, the person with the highest a priori risk of carrying a mutation in the gene should be tested. If there is a known mutation in the family, testing should begin with those family members with the highest risk of carrying the familial mutation.

Testing Logistics

Finding the appropriate laboratory to perform the testing is also very important. Genetic testing for most cancer susceptibility genes is available at a variety of laboratories in a variety of settings. It is important to note that many genetic tests can be done in a research lab as well as in a clinical laboratory. Clinical certification via the Clinical Laboratory Improvement Amendments of 1988 (CLIA), however, is essential when using the DNA tests for clinical management of the individual. When choosing a laboratory, it is also important to consider the fact that laboratory techniques (as well as sensitivity of the technique) vary. Finally, cost of testing as well as insurance coverage issues need to be taken

into account when choosing a laboratory to perform the genetic test.

The turnaround time for the genetic test will vary by gene and by laboratory. For most of the syndromes discussed in this chapter, genetic testing takes 4–12 weeks, and results are not available in enough time to impact the surgical management of a newly diagnosed breast cancer patient. There are two very important exceptions to this.

BRCA1/2 genetic test results are typically available within 14 days of the blood draw. The information gleaned from this has the potential to affect surgical decision-making if the results are available prior to definitive surgery. If a woman tests positive for a deleterious mutation, for example, she may choose mastectomy to treat her cancer and also undergo contralateral prophylactic mastectomy to reduce the risk of developing a second breast malignancy. Although women are interested in obtaining this genetics information at the time of diagnosis to help them plan their choice of surgery [40], women who report that they would not consider bilateral mastectomies even with a BRCA mutation are likely to proceed with breast-conserving surgery regardless of BRCA result [41].

Genetic testing for *TP53* mutations can take as little as 3 weeks if ordered as an "urgent" test. It is well known that *TP53* mutant cells are extremely sensitive to DNA damage [42, 43]. In vivo studies suggest that DNA damaging agents (e.g., chemotherapy and radiotherapy) used for treatment of a cancer in an individual with LFS can cause a second malignancy [44]. One study showed the risk of developing second cancer after radiotherapy treatment was as high as 57 % [45]. Although avoidance of chemotherapy in many situations is not plausible, radiotherapy can sometimes be avoided by different surgical techniques (e.g., mastectomy rather than lumpectomy for surgical treatment of breast cancer). It is important that oncologists realize that radiation should be avoided if possible (e.g., choosing mastectomy over lumpectomy). In many cases, however, radiation is needed for proper treatment of the current cancer, and in these cases, it should not be avoided. In these cases, it is imperative that the physicians and patient be aware of the risk of a second primary in the radiation field [44, 46].

For several reasons, it is important that the identification of women who are interested in and would use this genetic testing information in their surgical decision-making be done *prior to* any definitive treatment. First, when women undergo genetic counseling after definitive surgery, they are less likely to consider genetic testing pertinent to them [47]. Second, women may be subjected to additional surgical procedure and all of the associated risks. For example, one study showed that women who had *BRCA1/2* testing and who had initially undergone breast-conserving surgery chose to undergo subsequent bilateral mastectomies prior to receiving radiation therapy [48]. Finally, women with a family history of breast cancer may be advised to consider bilateral mastectomies for treatment of their newly diagnosed breast cancer. Most of these women if tested for BRCA mutations would find that they are not mutation carriers. Silva reported that in a group of such women, finding out that they are not mutation carriers *after* the prophylactic procedure leads many to question the decision to undergo prophylactic surgery. This, in turn, is often associated with complications and quality of life problems which they never envisioned [49].

Box 1.3 Components of Informed Consent

1. Purpose of the test and who to test
2. General information about the gene(s)
3. Possible test results
   - Positive result
   - Negative result: no mutation in the family (i.e., uninformative negative)
   - Negative results: known mutation in the family (i.e., true negative)
   - Variant of uncertain significance
4. Likelihood of positive result
5. Technical aspects and accuracy of the test
6. Economic considerations
7. Risks of genetic discrimination
8. Psychosocial aspects
   - Anticipated reaction to results
   - Timing and readiness for testing
   - Family issues
   - Preparing for results
9. Confidentiality issues
10. Utilization of test results
11. Alternatives to genetic testing
12. Storage and potential reuse of genetic material

Adapted from Trepanier et al. [31]

Informed Consent

Once a laboratory has been identified, it is necessary to obtain informed consent from the individual undergoing the test. The components and process of informed consent for cancer genetic testing have been described thoroughly [50–52] and are presented in Box 1.3. It is important to note that some US states have very specific laws that provide requirements as to what are the necessary components of the informed consent document itself.

Test Results and Follow-Up

Once the results are available, it is important to disclose the results to the patient in a timely fashion. The provider should review the significance of the results and quantify the

patient's risk for developing cancer, the emotional impact of the test results on the individual, screening recommendations and how his/her medical management should proceed given the test results, and the importance of sharing the information with his/her relatives and resources if desired [31].

It is incredibly important for the health-care provider and patient to maintain communication [31]. For those individuals who are found to carry a mutation in a cancer predisposition gene, the follow-up can ensure that the patient is adhering to appropriate screening recommendations and also ensure that there is dissemination of the test result through family. For individuals who are found to be "true negative," the future contact can ensure that the patient understands the appropriate screening (i.e., not too much screening but not avoidance of appropriate, general population screening recommendations). Patients receiving a "variant of uncertain significance" should stay in touch with the ordering provider so that if the variant is reclassified, that new information can be communicated quickly to the patient and his/her family.

For patients receiving an uninformative negative (i.e., a negative result when no mutation has been previously identified in the family), it is crucial to remain in contact with their genetics health-care provider. As new genetic tests become available, for example, the provider can advise whether or not these newer techniques are appropriate for them. The most appropriate method for recontacting patients has yet to be determined, and interestingly, the uptake of the additional testing was quite low in one study [53]. Nonetheless, every attempt to communicate with individuals should be made to ensure that they receive the best care.

This issue has come up twice in recent history with genetic testing for *BRCA1/2*. In 2002, Myriad Genetics labs introduced a newer technique for detecting mutations in *BRCA1*. Again in 2006, Myriad Genetics added a technique called "rearrangement testing" or "BART" which brought the sensitivity of the *BRCA1/2* test up to nearly 99 %. For those women who had testing prior to these newer technologies, it was important to communicate the availability of these tests so that they could decide to proceed with the additional test or not.

More recently in 2013, laboratories started offering "breast cancer gene panel" testing for patients. These tests include mutational analysis for many genes that have been associated with an increased risk of breast cancer. (Please see sections later in this chapter for full discussion of each gene.) Genetic counseling and testing for gene panels is more complex than testing for single gene disorders because of the length of time to obtain results, the higher likelihood of variants of uncertain significance, and the number of syndromes and associated cancer risks that need to be reviewed and the potential difficulty in management recommendations.

With single gene analysis, genetic counselors can discuss the specific disorder in depth and can focus on the patient's questions related to the syndrome. In gene panel testing, counselors are faced with reviewing multiple syndromes in a short period of time and synthesizing pertinent information about each syndrome or associated cancer risk without overwhelming the patient. Currently, test reporting can take anywhere from 2 to 6 months, so this type of testing may not be feasible for decision-making regarding surgical intervention or oncology treatment.

In addition, testing for multiple genes means that there is a higher risk for finding unclear results. With BRCA testing, for example, the number of variants of uncertain significance has decreased dramatically over time, with a rate of 5 % or less for patients of most ancestries [54]. With panel testing, many of these genes on the panels are not well characterized in any population. This means that the likelihood of finding a variant of uncertain significance is quite high when testing multiple genes in this setting. One laboratory that has been doing gene panel testing notes that the rate of finding at least one uncertain variant is over 30 % for its breast cancer gene panel testing (personal communication, Ambry Genetics Laboratories).

Because of the large number of genes that are "new" and therefore not well studied, there are many questions about how to manage individuals with deleterious mutations in these genes. Even in the genes that are considered to have well-defined cancer risks, management issues can be controversial. With high-risk breast cancer genes, there are often clear or at least published guidelines on how to follow and treat women with mutations in these genes. Typically, if a woman is tested for a particular single gene, it is usually because her personal and family history is consistent with the syndrome. With the approach of testing for multiple genes simultaneously, alterations may be found in genes that are not consistent with the history in the family or the individual. Consider the following example:

BRCA testing was negative in a woman with an invasive ductal breast cancer diagnosed at 45 who has multiple first- and second-degree relatives with early breast cancer. She meets with a genetic counselor to consider additional genetic testing and goes forward with breast cancer gene panel testing, and 3 months later, analysis reveals that she has a deleterious *CDH1* mutation, which is associated with Hereditary Diffuse Gastric Cancer (HDGC) syndrome. Standard management recommendations include prophylactic gastrectomy. Do you recommend this to your patient, knowing that she does not have the typical type of breast cancer seen in HDGC and has no family history of gastric cancer?

With more moderate-penetrance genes, there are generally few if any published guidelines on how to manage individuals with these types of gene mutations. Management strategies are even harder to determine in the "unknown" category of genes on these panels, which often have few studies to provide clinicians with evidence-based research.

Inherited Breast Cancer Syndromes

The identification of individuals with cancer predisposition gene mutations affords the mutation carriers the ability to use the information in making medical management decisions. The most clearly described hereditary breast cancer syndromes for which genetic testing is available include hereditary breast and ovarian cancer syndrome (HBOC), Cowden syndrome (CS), Li-Fraumeni syndrome (LFS), Peutz–Jeghers syndrome (PJS), and hereditary diffuse gastric carcinoma syndrome (HDGC). All of these syndromes are inherited in an autosomal dominant pattern and are associated with other cancers and clinical features. As noted previously in this chapter, genetic testing for each of the genes associated with these syndromes is available through commercial and research laboratories, thus allowing for appropriate clinical care, genetic counseling, and testing for at-risk individuals. Newer "breast cancer panel tests" include testing for lesser known genes and are discussed at length next.

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is the most common form of hereditary breast cancer and hereditary ovarian cancer. The vast majority of cases of HBOC are due to mutations in the *BRCA1* and *BRCA2* genes [21, 55]. *BRCA1* and *BRCA2* mutations are found in approximately 1 of 400 individuals but found more commonly in the Ashkenazi Jewish population in which 1 of 40 individuals carries one of three main disease-causing mutations: two in *BRCA1* (187delAG and 5385insC, previously named 185delAG and 5382insC) and the 6174delT mutation in *BRCA2* [56, 57]. Other founder mutations have been identified in populations that tend to be isolated by culture or geography [58, 59].

BRCA-associated cancers have been studied extensively. *BRCA2*-associated breast cancers are similar in phenotype and clinical behavior to sporadic breast cancers [60, 61]. *BRCA1*-related breast cancers are often of higher histological grade, show an excess of medullary histopathology, and are more likely than sporadic tumors to be "triple negative" (i.e., estrogen receptor negative, progesterone receptor negative, and are less likely to demonstrate HER2/neu overexpression) [62]. Ovarian cancers found in women with *BRCA1* and *BRCA2* mutations tend to be serous papillary cancers. Endometrioid and clear-cell subtypes of ovarian cancer have been observed [63], but borderline and mucinous ovarian tumors do not seem to be a part of the phenotype [64]. Both primary tumors of the fallopian tubes and peritoneum occur with increased frequency in mutation carriers [65]. The prognosis of ovarian cancer in *BRCA1* and *BRCA2* carriers is better than age-matched controls [63, 66, 67].

Table 1.3 BRCA1/2 cancer risks (lifetime risks)

Cancer site	BRCA1 mutation (%)	BRCA2 mutation (%)
Female breast	50–80	40–70
Ovarian cancer	<40	<20
Prostate	<30	<39
Pancreatic	1.3–3.2	2.3–7

Adapted from Ford et al. [55], King et al. [69], Antoniou et al. [74], Risch et al. [75], The Breast Cancer Linkage Consortium [76], and Ozcelik et al. [70]

The penetrance associated with mutations in *BRCA1* and *BRCA2* remains an active area of research. The range of breast cancer risk is influenced by the population under study: higher-risk estimates have come from studies with affected families and somewhat lower-risk estimates from studies in populations. Also, the risk of ovarian cancer is not the same for all *BRCA2* mutations, with mutations in the central 'ovarian cancer cluster region', conferring a higher lifetime risk [68]. Other factors, such as birth cohort, oral contraceptive use, age at first pregnancy, and exercise, have all been shown to influence penetrance risk in populations [69]. There has been a report of increased risk of gallbladder and bile duct, stomach, and melanoma with *BRCA2* mutation, none of which seem to be clinically actionable [70, 71]. Pancreatic cancer risk is also increased in families with *BRCA1* and especially *BRCA2* alterations, although studies differ as to the magnitude of this risk [72, 73]. The risks of developing specific cancers can be found in Table 1.3 [55, 69, 70, 74–76].

The current NCCN screening recommendations for women are listed in Box 1.4. Risk-reducing mastectomies are an appropriate consideration for women at the highest hereditary risk for breast cancer. Studies have shown a 90–95 % reduction in breast cancer risk following prophylactic mastectomy [77–80]. The evidence for the use of tamoxifen or raloxifene as chemopreventive agents in *BRCA* carriers is limited; however, tamoxifen has been shown to reduce the risk of contralateral breast cancers in *BRCA* carriers [81–83]. Two fairly recent studies support the role of risk-reducing salpingo-oophorectomy: the hazard ratio for ovarian cancer for women who underwent prophylactic surgery compared to those who chose close surveillance was 0.15 and 0.04, respectively [84, 85]. Women should be informed about the potential for the subsequent development of peritoneal carcinomatosis, which has been reported up to 15 years following RRBSO [65, 86].

Male *BRCA* mutation carriers face an increased risk for breast cancer and prostate cancer. They are advised to undergo training in breast self-examination with regular monthly practice and semiannual clinical breast examinations, and work-up of any suspicious breast lesions is recommended. The NCCN Guidelines® also recommend that a baseline mammogram be considered, with an annual mammogram if gynecomastia or parenchymal/glandular breast density is identified

Box 1.4 NCCN Screening for Female BRCA Carriers

- Breast awareness[a] starting at age 18 years
- Clinical breast exam, every 6–12 months,[b] starting at age 25 years
- Annual mammogram and breast MRI[c] screening starting at age 25, or individualized based on earliest age of onset in family[d]
- Discuss option of risk-reducing mastectomy.
  - Counseling may include a discussion regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy,[e] ideally between 35 and 40 years, and upon completion of child bearing, or individualized based on earliest age of onset of ovarian cancer in the family.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy to a recommended maximum age of natural menopause, and related medical issues.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
- For those patients who have not elected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound (preferably days 1–10 of menstrual cycle in premenopausal women) + CA-125 (preferably after day 5 of menstrual cycle in premenopausal women)[f] every 6 months starting at age 30 years or 5–10 years before the earliest age of first diagnosis of ovarian cancer in the family.
- Consider chemoprevention options for breast and ovarian cancer, including discussing risks and benefits[g] (see NCCN guidelines for breast cancer risk reduction).
- Consider investigational imaging and screening studies, when available (e.g., novel imaging technologies, more frequent screening intervals), in the context of a clinical trial.

[a]Women should be familiar with their breasts and promptly report changes to their health-care provider. Periodic, consistent breast self-examination (BSE) may facilitate breast self-awareness. Premenopausal women may find BSE most informative when performed at the end of the menses

[b]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6–12 months is the concern for interval breast cancers

[c]High-quality MRI limitations include having a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women

[d]The best screening strategy for women age 25–30 is uncertain with some data suggesting that mammogram be added to MRI only after age 30. The appropriateness of imaging modalities and scheduling is still under study [225]

[e]Given the high rate of occult neoplasms, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (See discussion for details.) See the College of American Pathologists, Protocol for the Examination of Specimens from patients with Carcinoma of the Ovary

[f]There are data that show that annual transvaginal ultrasound and CA-125 are not effective strategies for screening for ovarian cancer in high-risk women. There are limited data regarding the effectiveness of a 6-month screening interval. Thus, until such data are available, it is reasonable to consider this approach in high-risk women, especially in the context of a clinical research setting

[g]Data suggest that oral contraceptives (OCs) reduce ovarian cancer risk in BRCA mutation carriers. The risk/benefit ratio is uncertain because of contradictory evidence about OC's increasing breast cancer risk; however, OC use for contraception is acceptable. Other chemoprevention options for breast cancer include tamoxifen and raloxifene; however, only very limited data with these agents are available in patients with BRCA mutations. (See discussion for details.)

on baseline study [1]. The guidelines also recommend that male BRCA mutation carriers should adhere to the current prostate cancer screening guidelines [1, 87].

Li-Fraumeni Syndrome [88]

Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome that is thought to be responsible for ~1 % of breast cancer [89]. LFS is often thought of as a hereditary predisposition to cancer in general, involving many tumor types and occurring at any point in an individual's lifetime, often early adult and childhood cancers. The majority of cases of LFS are due to mutations in the *TP53* gene [90–93]. The component tumors of LFS include bone sarcomas (primarily osteosarcomas and chondrosarcomas), soft-tissue sarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinomas [94]. The classic component tumors are thought to account for 63–77 % of cancer diagnoses in individuals with Li Fraumeni syndrome [94–97]. Breast cancer is the most common tumor

Box 1.5 Other Tumors Associated with LFS

Wilms' tumor
Malignant phyllodes tumor
Lung cancer
Choroid plexus tumor
Colorectal cancer
Prostate cancer
Pancreatic cancer
Bladder cancer
Hepatoblastoma
Neuroblastoma
Lymphomas
Nasopharyngeal cancer
Teratomas
Ureteral tumors
Testicular cancer
Laryngeal cancer
Ovarian cancer
Melanoma
Gonadal germ cell tumors
Stomach cancer

Adapted from Gonzalez et al. [95], Nichols et al. [96], Hwang et al. [97], Kleihues et al. [98], Olivier et al. [99], Birch et al. [100], and Strong et al. [101]

in *TP53* mutation carriers (24–31.2 %), followed by soft tissue sarcomas (11.6–17.8 %), brain tumors (3.5–14 %), osteosarcomas (12.6–13.4 %), and adrenocortical tumors (6.5–9.9 %) [98, 99]. Other tumors that have been argued to be component tumors of LFS are listed in Box 1.5 [95–101].

There are some data regarding common histology of LFS component tumors. Breast cancers are most commonly invasive ductal carcinomas and may have a tendency toward being "triple positive" [94, 102]. Rhabdomyosarcomas account for 55 % of soft-tissue sarcomas, followed by fibrosarcomas (13 %), and then malignant fibrous histiocytomas [98]. For LFS-associated brain tumors, 69 % are astrocytic (astrocytoma or glioblastoma), followed by medulloblastoma/PNET tumors (17 %) [98].

Typically, LFS-associated tumors occur at significantly younger ages than when they occur sporadically. However, depending on tumor type, the mean age of diagnosis varies from childhood well into adulthood [98]. Understanding cancer risk for LFS is somewhat complicated as the ranges of risk vary greatly between studies and depend largely on study population. When pooling studies that examine overall cancer risk in *TP53* mutation carriers (both female and male), the risk of developing cancer by ages 15–20 is 12–42 %, by ages 40–45 is 52–66 %, by age 50 is 80 %, and by age 85 is 85 % [96, 97, 103, 104]. When separating out the sexes, it is apparent that female *TP53* mutation carriers have generally a higher lifetime cancer risk in comparison to males [97, 104, 105].

Individuals diagnosed with LFS are also at markedly increased risk to develop multiple primary tumors. Hisada et al. found that following a first cancer diagnosis, there is a 57 % risk for a second primary tumor within 30 years of the first diagnosis, followed by a 38 % risk for a third primary tumor within 10 years of the second cancer diagnosis [45]. In addition, it has been widely observed that second, third, etc. primary cancers commonly occur in the radiation field of previously treated cancers [45, 90, 94, 104].

Currently, NCCN management recommendations (Box 1.6) for individuals with LFS center around proven screening techniques such as mammography and MRI for the detection of breast cancer and early colonoscopy [88]. Because of the wide variety of tumors that can be seen in LFS, researchers have begun to consider whole-body imaging techniques such as MRI or PET scans for individuals who have *TP53* mutations. One study published in 2011 involved the use of whole-body MRI, in addition to certain targeted MRI screening and biochemical testing, to screen children and adults with LFS. Researchers were successful in detecting cancers presymptomatically and early [106]. While this cohort was relatively small, promising studies like these give hope to families with Li-Fraumeni syndrome for the possibility of screening and detecting cancers at an earlier, curable stage.

Cowden Syndrome

Cowden syndrome (CS) is a rare hereditary cancer syndrome that is characterized by overgrowth in different organ systems. The incidence of CS is thought to be about 1 in 200,000 but may be underdiagnosed. CS belongs to the set of syndromes known as the *PTEN* hamartoma tumor syndromes (PHTS) [107]. *PTEN* (phosphatase and tensin homolog) mutations are found in the vast majority of patients with Cowden syndrome, although mutations in other genes such as *BMPR1A* and the succinate dehydrogenase (SDH) genes have been reported in a small number of patients who have features of Cowden syndrome but do not meet diagnostic criteria (Cowden syndrome like) [108, 109].

Diagnostic criteria for Cowden syndrome are complicated [110]. The National Comprehensive Cancer Network's (NCCN) most recent NCCN guidelines (v.4.2013) for testing for Cowden syndrome are included in Box 1.7 [88].

Breast cancer is the most frequent cancer seen in Cowden syndrome. Reports of the risk of cancers associated with CS vary widely [111, 112]. It was initially felt that Cowden syndrome patients faced moderate increased risks for cancer; however, a paper published in 2012 by a group from the Cleveland Clinic reported much higher risks for cancer than previously thought. In 2013, the French Cowden disease network published similar high risks for cancer

Box 1.6. NCCN Screening for Li-Fraumeni Syndrome

Breast cancer risk, women

- Breast awareness[a] starting at age 18 years
- Clinical breast exam, every 6–12 months, starting at age 20–25 years or 5–10 years before the earliest known breast cancer in the family (whichever comes first).
- Annual mammogram and breast MRI screening starting at 20–25 years[b] or individualized based on earliest age of onset in family[c,d]
- Discuss risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy.

Other Cancer Risks

- Address limitations of screening for many cancers associated with LFS. Because of the remarkable risk of additional primary neoplasms, screening may be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).
- Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors includes careful skin and neurologic examinations.
- Therapeutic RT for cancer should be used with caution.
- Consider colonoscopy every 2–5 years starting no later than 25 years.
- Pediatricians should be apprised of the risk of childhood cancers in affected families.
- Discuss option to participate in novel screening approaches using technologies within clinical trials when possible, such as whole-body MRI, abdominal ultrasound, and brain MRI.[e]
- Additional surveillance based on individual family histories.
- Education regarding signs and symptoms of cancer.

Risk to Relatives

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Reproductive Options

- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See discussion for details.

[a]Women should be familiar with their breasts and promptly report changes to their health-care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self-awareness. Premenopausal women may find BSE most informative when performed at the end of the menses

[b]Given theoretical concerns with harmful effects of radiation exposure in LFS, for patients aged 20–30 years, annual MRI-only screening may be sufficient based on physician's discretion

[c]The appropriateness of imaging modalities and scheduling is still under study

[d]High-quality MRI limitations include having a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women

[e]A surveillance study has been published that utilizes these screening approaches [106]

in carriers [113]. See Table 1.4. There is a possibility of ascertainment bias in these more recent papers because of recruitment strategies. The screening recommendations for individuals with Cowden synrome are seen in Box 1.8.

Table 1.4 French Cowden disease network published high risks for cancer in carriers

	Pilarski (2009) [111]	Tan et al. (2012) [112]	Bubien et al. (2013) [113]
Breast cancer risk	25–50 %	85 %	77 %
Thyroid cancer	3–10 %	35 %	38 %
Endometrial cancer	5–10 %	28 %	NS
Renal cell cancer	Unknown	34 %	NS
Melanoma	Unknown	6 %	NS
Colorectal cancer	Unknown	9 %	NS

Adapted from Pilarski [111], Tan et al. [112], Bubien et al. [113]
NS not specified

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant gastrointestinal polyposis syndrome. The incidence is not well known but is estimated at 1 in 25,000 to 1 in 300,000

Box 1.7 NCCN Guidelines for Testing for Cowden Syndrome (v.4.2013)

- Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Adult Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum)
- Autism spectrum disorder and macrocephaly or
- ≥2 biopsy-proven trichilemmomas
- ≥2 major criteria (one must be macrocephaly)
- ≥3 major criteria, without macrocephaly or
- 1 major and ≥3 minor criteria
- ≥4 minor criteria
- Fewer criteria are needed when an individual has a relative with a clinical diagnosis of Cowden syndrome (any one major criteria or two minor criteria)

Major criteria

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly (≥97th percentile, 58 cm in adult women, 60 cm in adult men)
- Macular pigmentation of glans penis
- Mucocutaneous lesions
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

Minor criteria

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥3)
- Lipomas
- Mental retardation (intelligence quotient ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (e.g., adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

Box 1.8 NCCN Guidelines for Cancer Screening and Prevention: Cowden Syndrome

Women

- Breast awareness starting at age 18 years
- Clinical breast exam, every 6–12 months, starting at age 25 years or 5–10 years before the earliest known breast cancer in the family.
- Annual mammography and breast MRI screening starting at age 30–35 years or 5–10 years before the earliest known breast cancer in the family (whichever comes first).
- For endometrial cancer screening, encourage patient education and prompt response to symptoms and participation in a clinical trial to determine the effectiveness and necessity of screening modalities.
- Discuss option of risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and hysterectomy and/or hysterectomy.

Men and women

- Annual comprehensive physical exam starting at age 18 or 5 years before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to breast and thyroid exams.
- Baseline thyroid ultrasound at age 18 years and consider annually thereafter.
- Consider colonoscopy starting at age 35 years, then every 5–10 years or more frequently if patient is symptomatic or polyps found.
- Consider annual dermatologic exam.
- Education regarding the signs and symptoms of cancer.

Risk to relatives

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Reproductive options

- For women of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See discussion for details.

live births by the National Institutes of Health [114]. Peutz-Jeghers is characterized by the development of Peutz-Jeghers polyps (a specific type of hamartoma) in the intestine in conjunction with pigmentation (brown or bluish spots) around and inside the mouth, nose and lips, perianal area, as well as other parts of the body. The mucocutaneous lesions are often most prominent in childhood and fade with age.

Most families with PJS have mutations in the *STK11* gene, although this gene does not explain all inherited cases of PJS as well as many simplex cases [115]. The lifetime risk of breast cancer in females with PJS is reported in a wide range, with the most consistent risks being in the 30–50 % range [116, 117]. Other cancers that can be seen in PJS include cancers of the colon, pancreas, stomach, ovary, small intestine, lung, cervix, testes, uterus, and esophagus [118]. Consensus diagnostic criteria were published in 2010 and are listed in Box 1.9 [118]. Screening and surveillance guidelines are also included in Table 1.5 [119].

Box 1.9 Clinical Diagnostic Criteria for Peutz-Jeghers

Any *ONE* of the following is present:

- Two or more histologically confirmed PJ polyps
- Any number of PJ polyps detected in one individual who has a family history of PJS in close relative(s)
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in close relative(s)
- Any number of PJ polyps in an individual who also has characteristic mucocutaneous pigmentation

Adapted from Beggs et al. [118]

Hereditary Diffuse Gastric Cancer Syndrome

Hereditary diffuse gastric cancer syndrome is a rare autosomal dominant hereditary cancer syndrome characterized by diffuse or signet ring cell pathology cancer of the stomach. The incidence of this syndrome is not well known. The lifetime risk of stomach cancer is thought to be approximately 80 % compared to less than 1 % in the general population [120, 121]. The second most common cancer in families with this syndrome is lobular breast cancer, with a lifetime risk of about 40 % in women [122–126]. Colorectal cancer and cleft lip and palate have also been reported in some families [123, 127]. The International Gastric Cancer Linkage Consortium (IGCLC) published clinical criteria in 2010 seen in Box 1.10 [128]. Screening and prevention adapted from consensus guidelines are included in Box 1.11 as well [129].

Box 1.10 Clinical Criteria for Hereditary Diffuse Gastric Cancer Syndrome

Any of the following:

- Two gastric cancer (GC) cases in a family, one individual under age 50 years with confirmed diffuse gastric cancer (DGC)
- Three confirmed DGC cases in first- or second-degree relatives independent of age
- Simplex case (i.e., a single occurrence in a family) of DGC occurring before age 40 years
- Personal or family history of DGC and lobular breast cancer, one diagnosed before age 50 years

Adapted from Fitzgerald et al. [128]

Table 1.5 NCCN screening and surveillance guidelines for Peutz-Jeghers syndrome

Site	Procedure	Onset (year)	Interval (year)
Stomach	Upper endoscopy[a]	8	2–3
Small intestine	Capsule endoscopy or MR enterography[b]	8	2–3
Large intestine	Colonoscopy	18	2–3
Breast	Breast examination	25[c]	Monthly
	Mammography or MRI	25[c]	1
Ovary	Transvaginal ultrasound and serum CA 125[c]	18	1
Cervix and uterus	Pelvic exam with Pap smear[d]	18	1
Pancreas	MRI-MRCP or endoscopic ultrasound and CA 19-9	25	1–2
Testes	Testicular exam; ultrasound if symptomatic or abnormality on exam	Birth	1

[a]Extended upper endoscopy beginning at age 18 years

[b]CT enterography as alternative

[c]Discuss prophylactic mastectomy

[d]Discuss prophylactic hysterectomy and oophorectomy

Box 1.11 Consensus Screening and Prevention Guidelines for CDH1 + Patients

Consider prophylactic gastrectomy with close nutritional follow-up.
If refused, annual EGD with biopsy
If biopsy is positive for signet ring cells, recommend prophylactic gastrectomy and close nutritional follow-up.
Screening for lobular breast cancer from age 35 years
Consider colorectal cancer screening in families with CRC beginning at age 40 years or 10 years younger than the earliest case.

Adapted from Fitzgerald et al. [128]

Moderate- and Low-Penetrance Breast Cancer Genes

Besides the high-risk genes and syndromes listed previously, several familial forms of breast cancer have been reported. These include families with *CHEK2* and *ATM* mutations. The risk of breast cancer associated with alterations in these genes is thought to be lower than with traditional hereditary breast cancer syndromes; other factors are likely to interact with the effects of changes in these genes and result in a more moderate increase in risk for breast cancer.

Researchers at the University of Washington published a study on germline mutations in 12 genes linked to ovarian cancer that are also being analyzed in families with breast cancer [130–132]. Many laboratories are offering genetic testing for panels of genes that are important in DNA repair pathways. This grouping is adapted and expanded from categories presented by Pennington and Swisher in 2012 [133].

Group 1: Genes Functionally Related to BRCA1 and BRCA2 (ATM, BARD1, CHEK2, MRE11A, NBN, RAD50, FAM175A)

ATM (Ataxia Telangiectasia Mutated)

ATM is a serine threonine kinase that mediates checkpoint regulation and homologous repair [134]. *ATM*-deficient cells display increased chromosome breakage and abnormal cell cycle progression, especially in the presence of ionizing radiation. An increased risk for breast cancer was first observed in the mothers of patients with ataxia telangiectasia (a recessive condition characterized by cerebellar ataxia, telangiectasias, immune deficiency, and a high risk of cancer) more than 30 years ago [135]; breast cancer is also seen more often in A-T patients [136]. The relative risk of breast cancer for *ATM* mutation carriers is thought to be about 2.4-fold over that of noncarriers [137].

BARD1 (BRCA1-Associated RING Domain 1)

BARD1 helps to mediate the tumor suppressor function of *BRCA1* and has an independent role in tumor suppression as well. Initial studies on *BARD1* seemed to indicate a higher frequency of mutations in familial breast cancer or breast/ovarian cancer than in controls, although the significance of these mutations was unclear [138, 139]. Clearly deleterious mutations of *BARD1* have been reported in families with breast and/or ovarian cancer, but in a small percentage of cases [140]. Relative risks for breast cancer are not well known.

CHEK2 (Cell Cycle Checkpoint Kinase 2)

CHEK2 is a serine threonine kinase involved in double-strand DNA break repair. *CHEK2* was initially reported in a few families with a clinical diagnosis of Li-Fraumeni syndrome but does not play a major role in LFS [141, 142]. Several different mutations have been reported to be associated with increased breast cancer risk; one specific common mutation in *CHEK2*, 1100delC, appears to confer about a 2.4-fold increase in breast cancer risk [143]. The interaction of 1100delC with family history of breast cancer yields a relative risk of almost fivefold (approximately 37 % by age 70) [143]. Women who are homozygous for 1100delC seem to have an even higher risk for breast cancer and multiple primary tumors [144]. The carrier frequency of 110delC is higher in some European populations than in North America and, consequently, support for widespread testing of this mutation is more common in Europe than in the USA [131, 145].

MRE11A (Meiotic Recombination 11 Homolog A, S. Cerevisiae)

Recessively inherited mutations in *MRE11A* cause ataxia-telangiectasia-like disorder (ATLD), another chromosomal instability syndrome. *MRE*11A is part of an important complex along with Rad50 and Nbn/Nbs1, called MRN, which is critical for genomic integrity and tumor suppression. *MRE11A* germline mutations were found in a small number of women whose breast tumors showed loss or reduction of all three MRN complex proteins [146]. Few studies have analyzed the risk of breast cancer associated with mutations in this gene.

NBN (Nibrin aka NBS1)

Nijmegen breakage syndrome is a recessively inherited chromosomal instability syndrome characterized by microcephaly, growth retardation, immune deficiency, and cancer caused by alterations in *NBN* (OMIM #251260). Two common mutations, 657del5 and R215W, have been seen in Slavic cancer populations and at low frequency in controls [147, 148]. The relative risk of breast cancer in this

population appears to be about threefold higher in carriers of the 657del5 mutation [149]. A germline missense mutation, Leu150Phe, has been reported in a small number of Northern European breast cancer families [150]. However, deleterious mutations have not been found in other populations [151, 152].

RAD50

One patient has been reported with Nijmegen breakage syndrome-like disorder (NBSLD), another recessively inherited chromosomal instability syndrome; she was found to be a compound heterozygote for mutations in *RAD50* (OMIM #613078 [151]). *RAD50* mutations have been reported in similar cohorts as *NBN* [150]. The significance of a previously reported mutation, 687delT, found in Finnish families, has been challenged [153]. *RAD50* mutations have not been seen consistently in other populations [151, 154, 155]. Therefore, the relative risk of breast cancer associated with carriers of *RAD50* mutations is unknown.

FAM175A (Family with Sequence Similarity 175, Member A aka ABRA1, CCDC98)

FAM175A produces a BRCA1-associated protein that links BRCA1 to a core complex dedicated to ubiquitin chain recognition and hydrolysis at DNA double-strand breaks. One study indicates that mutations in this gene may be linked with a rare form of hereditary breast cancer in Finnish families [156].

Group 2: Other Genes in the Fanconi Anemia Pathway That Increase Breast Cancer Risk (BRIP1, PALB2)

BRIP1(BRCA-Interacting Protein C-Terminal Helicase 1 or FANCJ)

BRIP1 is important in the double-strand DNA repair function of *BRCA1*. Seal and colleagues published a report in 2006 which showed truncating mutations in 9/1,212 women with breast cancer and 2/2,081 controls [157]. They calculated a relative risk of 2.0 associated with a truncating *BRIP1* mutation. Several studies have shown a low frequency of *BRIP1* mutation in various cohorts, but often the mutation does not segregate with cancer in the family [158–161]. Many studies have not observed a link between *BRIP1* and breast or ovarian cancer risk [162–167]. It is unclear whether the relative risk of 2 for breast cancer is accurate, but if there is an association, it is likely to be a small one for most populations. There are specific founder mutations which seem to confer a much higher risk for cancer; for example, an Icelandic *BRIP1* mutation, c.2040_2041insTT, confers an odds ration of ~8 for ovarian cancer [168].

PALB2 (Partner and Localizer of BRCA2 or FANCN)

PALB2 co-localizes with BRCA2 in the nucleus and helps to stabilize the protein, making it critical for homologous recombination [169]. *PALB2* mutations were first reported in breast cancer patients in 2007; a link between breast cancer and pancreatic cancer has also been seen. A UK group found a frequency of mutation of ~1 % in familial breast cancer cases (10/923 versus 0/1,084 controls); they estimated a twofold increase in risk for breast cancer [170]. In Finland, a founder mutation, c.1592delT, was seen in ~1 % of unselected breast cancer cases and 2.7 % of familial breast cancer cases [171]. In greater than 20 studies, the frequency of *PALB2* mutations in breast cancer cohorts varies from 0 to 5 %, with most populations having a frequency of 0.5–1 % in cases [161, 172–197]. The Finnish mutation (c.1592delT) may be more highly penetrant than other mutations with an estimated lifetime risk of 40 % by age 70 with triple-negative tumors seen more often [190, 198]. There is a question of whether the location of the truncating mutation has differential effects on breast cancer risk [198].

Group 3: RAD51 Gene Family Members

RAD51 Paralogs

RAD51 is a critical part of DNA repair through homologous recombination [199]. Members of the *RAD51* gene family which share homology to *RAD51* and each other are also important in homologous recombination and have independent DNA repair functions; these *RAD51* paralogs include *RAD51B*, *RAD51C*, *RAD51D*, *XRCC2*, and *XRCC3* [200]. While RAD51 mutations have not been linked with hereditary cancer, associations have been made with several gene family members. *RAD51C* has been implicated in one family with Fanconi anemia-like phenotype and is likely to represent one of the Fanconi anemia complementation groups (FANCO) [201]. *RAD51C* and *RAD51D* mutations have been found in women with ovarian cancer [202–207]. While *RAD51C* and *RAD51D* mutations appear to be relatively rare, families with mutations in these genes (especially *RAD51D*) could represent a small but important fraction of hereditary ovarian cancer. The risk of breast cancer associated with *RAD51C* and *RAD51D* mutations is not well known, but they do not appear to be major contributors to risk. One study which analyzed 689 multiple breast cancer case families through whole exome sequencing reported two families with *XRCC2* mutations, one protein-truncating mutation and one missense [208]. However, a larger analysis of 3,548 familial breast cancer cases and 1,435 controls did not find any evidence of *XRCC2* mutations as causative in cases [209]. One particular SNP in *XRCC3*, T241M, found

in about 10 % of Asian women has been associated with a moderate increase in risk for breast cancer [210, 211]. An SNP in *RAD51B* has been associated with a modest increase in risk for male breast cancer [212]. Yet, a larger study of *RAD51B* on multiple-case, non-BRCA families did not reveal any germline mutations [213].

Group 4: Hereditary Colorectal Cancer/ Polyposis Genes

Lynch Syndrome and MYH-Associated Polyposis

Lynch syndrome (LS) is the most common hereditary form of colorectal cancer accounting for about 2–3 % of colorectal cancer cases. It is caused by mutations in genes involved in DNA mismatch repair, including *MLH1*, *MSH2*, *MSH6*, *PMS2*, and, indirectly, *EPCAM*. LS is typically characterized by the development of relatively early onset colorectal and uterine cancer; increased risks for other cancers include stomach cancer, cancer of the small intestine, pancreatic cancer, sebaceous carcinomas, ovarian cancer, cancers of the urinary collecting tract, and rarely brain tumors [214]. Most studies have not shown a significant increase in breast cancer risk for MMR mutation carriers versus noncarriers [215], although a more recent paper studying a cohort of Lynch syndrome families prospectively did show a fourfold increase in breast cancer risk [216]. It is clear that defective mismatch repair can be seen in some breast cancers in women from Lynch syndrome families [217, 218]. Whether there is a true increase in risk (and the magnitude of this risk) is a matter of debate at this point.

MUTYH-associated polyposis (MAP) is a recessive form of adenomatous polyposis. *MUTYH* is involved in base excision repair; without MUTYH, oxidative DNA damage leads to the formation of 8-oxo-G which mispairs with adenine. This leads to an increase in G:C>T:A transversions in *APC* and other genes [219]. MAP is associated with an attenuated phenotype; adenomas typically number less than 100 and a mixture of polyp types (serrated adenomas, hyperplastic polyps) and duodenal polyps are often seen [220, 221]. Extraintestinal manifestations, including breast cancer, have been reported in MAP [222, 223]. However, *MUTYH* does not appear to be a common cause of breast cancer [224].

Summary

Cancer genetics has become an integral subspecialty of the practice of preventive medicine and oncology. Genetic counselors provide expertise in the attainment of the family history, cancer risk assessment, and guidance for individuals as they pursue genetic testing through the informed consent process. The identification of individuals who harbor mutations in cancer predisposition genes enables the utilization of appropriate screening and prevention techniques. Cancer genetic care begins with the identification of individuals at high risk, proceeds through the genetic counseling and testing process, and culminates in targeted and effective medical management for these individuals. As genetic testing becomes more routine, the hope is that information about hereditary and familial cancer predisposition will lead to the development of better screening techniques, earlier detection, less morbidity from preventive options, and longer disease-free survival.

References

1. NCCN guidelines: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High – Risk Assessment: Breast and Ovarian V.4.2013. http://www.nccn.org.
2. Pal T, Vadaparampil ST. Genetic risk assessments in individuals at high risk for inherited breast cancer in the breast oncology care setting. Cancer Control. 2012;19(4):255–66.
3. Sifri R, et al. Use of cancer susceptibility testing among primary care physicians. Clin Genet. 2003;64(4):355–60.
4. Wideroff L, et al. Physician use of genetic testing for cancer susceptibility: results of a national survey. Cancer Epidemiol Biomarkers Prev. 2003;12(4):295–303.
5. Acheson LS, et al. Validation of a self-administered, computerized tool for collecting and displaying the family history of cancer. J Clin Oncol. 2006;24(34):5395–402.
6. Sweet KM, Bradley TL, Westman JA. Identification and referral of families at high risk for cancer susceptibility. J Clin Oncol. 2002;20(2):528–37.
7. Drohan B, et al. Hereditary breast and ovarian cancer and other hereditary syndromes: using technology to identify carriers. Ann Surg Oncol. 2012;19(6):1732–7.
8. Simon C, et al. Patient interest in recording family histories of cancer via the internet. Genet Med. 2008;10(12):895–902.
9. Reid GT, et al. Family history questionnaires designed for clinical use: a systematic review. Public Health Genomics. 2009;12(2):73–83.
10. Hilgart JS, Coles B, Iredale R. Cancer genetic risk assessment for individuals at risk of familial breast cancer. Cochrane Database Syst Rev. 2007;(2):CD003721.
11. ASCO. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. 2003;21(12):2397–406.
12. Giardiello FM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. N Engl J Med. 1997;336(12):823–7.
13. Miller C. The value of genetic counselors in the laboratory. ARUP Laboratories; Salt Lake City, UT, 2011.
14. Berliner JL, et al. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J Genet Couns. 2013;22(2):155–63.
15. Riley BD, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. J Genet Couns. 2012;21(2):151–61.
16. Gail MH, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879–86.
17. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer. 1994;73(3):643–51.

18. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004; 23(7):1111–30.
19. Berry DA, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol. 2002;20(11):2701–12.
20. MacKarem G, Roche CA, Hughes KS. The effectiveness of the Gail model in estimating risk for development of breast cancer in women under 40 years of age. Breast J. 2001;7(1):34–9.
21. Frank TS, et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol. 1998;16(7):2417–25.
22. Couch FJ, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med. 1997;336(20): 1409–15.
23. Shattuck-Eidens D, et al. BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA. 1997;278(15):1242–50.
24. Kang HH, et al. Evaluation of models to predict BRCA germline mutations. Br J Cancer. 2006;95(7):914–20.
25. Barcenas CH, et al. Assessing BRCA carrier probabilities in extended families. J Clin Oncol. 2006;24(3):354–60.
26. James PA, et al. Optimal selection of individuals for BRCA mutation testing: a comparison of available methods. J Clin Oncol. 2006;24(4):707–15.
27. Tan MH, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet. 2011;88(1):42–56.
28. Saslow D, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin. 2007;57(1):7–28.
29. Bennett RL, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17(5): 424–33.
30. Bennett RL, et al. Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. Am J Hum Genet. 1995;56(3):745–52.
31. Trepanier A, et al. Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. J Genet Couns. 2004;13(2):83–114.
32. Kumaravel V, et al. Patients do not recall important details about polyps, required for colorectal cancer prevention. Clin Gastroenterol Hepatol. 2012;11(5):543–7 e1-2.
33. Jefferies S, Goldgar D, Eeles R. The accuracy of cancer diagnoses as reported in families with head and neck cancer: a case-control study. Clin Oncol (R Coll Radiol). 2008;20(4):309–14.
34. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA. 2004;292(12):1480–9.
35. Chang ET, et al. Reliability of self-reported family history of cancer in a large case-control study of lymphoma. J Natl Cancer Inst. 2006;98(1):61–8.
36. Mai PL, et al. Prevalence of family history of breast, colorectal, prostate, and lung cancer in a population-based study. Public Health Genomics. 2010;13(7–8):495–503.
37. Ozanne EM, et al. Bias in the reporting of family history: implications for clinical care. J Genet Couns. 2012;21(4):547–56.
38. Ziogas A, et al. Clinically relevant changes in family history of cancer over time. JAMA. 2011;306(2):172–8.
39. Schneider KA. Counseling about cancer: strategies for genetic counseling. 2nd ed. New York: Wiley-Liss; 2002. xviii, 333 p.
40. Schwartz MD, et al. Impact of BRCA1/BRCA2 counseling and testing on newly diagnosed breast cancer patients. J Clin Oncol. 2004;22(10):1823–9.
41. Ray JA, Loescher LJ, Brewer M. Risk-reduction surgery decisions in high-risk women seen for genetic counseling. J Genet Couns. 2005;14(6):473–84.
42. Liang L, et al. Radiation-induced genetic instability in vivo depends on p53 status. Mutat Res. 2002;502(1–2):69–80.
43. Shay JW, et al. Spontaneous in vitro immortalization of breast epithelial cells from a patient with Li-Fraumeni syndrome. Mol Cell Biol. 1995;15(1):425–32.
44. Heyn R, et al. Second malignant neoplasms in children treated for rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. J Clin Oncol. 1993;11(2):262–70.
45. Hisada M, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst. 1998;90(8):606–11.
46. Salmon A, et al. Rapid development of post-radiotherapy sarcoma and breast cancer in a patient with a novel germline "de-novo" TP53 mutation. Clin Oncol (R Coll Radiol). 2007;19(7): 490–3.
47. Vadaparampil ST, et al. Experiences of genetic counseling for BRCA1/2 among recently diagnosed breast cancer patients: a qualitative inquiry. J Psychosoc Oncol. 2008;26(4):33–52.
48. Stolier AJ, Corsetti RL. Newly diagnosed breast cancer patients choose bilateral mastectomy over breast-conserving surgery when testing positive for a BRCA1/2 mutation. Am Surg. 2005;71(12): 1031–3.
49. Silva E. Genetic counseling and clinical management of newly diagnosed breast cancer patients at genetic risk for BRCA germline mutations: perspective of a surgical oncologist. Fam Cancer. 2008;7(1):91–5.
50. Bernhardt BA, et al. Toward a model informed consent process for BRCA1 testing: a qualitative assessment of women's attitudes. J Genet Couns. 1997;6(2):207–22.
51. Geller G, et al. Genetic testing for susceptibility to adult-onset cancer. The process and content of informed consent. JAMA. 1997;277(18):1467–74.
52. Geller G, et al. "Decoding" informed consent. Insights from women regarding breast cancer susceptibility testing. Hastings Cent Rep. 1997;27(2):28–33.
53. Shannon KM, et al. Uptake of BRCA1 rearrangement panel testing: in individuals previously tested for BRCA1/2 mutations. Genet Med. 2006;8(12):740–5.
54. Eggington JM, Burbidge LA, Roa B, Pruss D, Bowles K, Rosenthal E, Esterling L, Wenstrup R. Current variant of uncertain significance rates in BRCA1/2 and lynch syndrome testing (MLH1, MSH2, MSH6, PMS2, EPCAM). American College of Medical Genetics and Genomics annual meeting, Charlotte, NC, Mar 2012.
55. Ford D, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998;62(3): 676–89.
56. Struewing JP, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336(20):1401–8.
57. Kauff ND, et al. Incidence of non-founder BRCA1 and BRCA2 mutations in high risk Ashkenazi breast and ovarian cancer families. J Med Genet. 2002;39(8):611–4.
58. Thorlacius S, et al. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet. 1996;13(1):117–9.
59. Unger MA, et al. Screening for genomic rearrangements in families with breast and ovarian cancer identifies BRCA1 mutations previously missed by conformation-sensitive gel electrophoresis or sequencing. Am J Hum Genet. 2000;67(4):841–50.
60. Chappuis PO, Nethercot V, Foulkes WD. Clinico-pathological characteristics of BRCA1- and BRCA2-related breast cancer. Semin Surg Oncol. 2000;18(4):287–95.

61. Phillips KA, Andrulis IL, Goodwin PJ. Breast carcinomas arising in carriers of mutations in BRCA1 or BRCA2: are they prognostically different? J Clin Oncol. 1999;17(11):3653–63.
62. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. J Clin Oncol. 2008;26(15):2568–81.
63. Boyd J, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA. 2000;283(17):2260–5.
64. Lakhani SR, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res. 2004;10(7):2473–81.
65. Levine DA, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol. 2003;21(22):4222–7.
66. Cass I, et al. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer. 2003;97(9):2187–95.
67. Arun B, et al. Response to neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and noncarriers: a single-institution experience. J Clin Oncol. 2011;29(28):3739–46.
68. Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet. 2001;68(2):410–9.
69. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302(5645):643–6.
70. Ozcelik H, et al. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. Nat Genet. 1997;16(1):17–8.
71. van Asperen CJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42(9):711–9.
72. Mocci E, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. Cancer Epidemiol Biomarkers Prev. 2013;22(5):803–11.
73. Iqbal J, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2012;107(12):2005–9.
74. Antoniou A, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72(5):1117–30.
75. Risch HA, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68(3):700–10.
76. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91(15):1310–6.
77. Hartmann LC, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93(21):1633–7.
78. Rebbeck TR, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004;22(6):1055–62.
79. Meijers-Heijboer H, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(3):159–64.
80. Robson M, et al. Appropriateness of breast-conserving treatment of breast carcinoma in women with germline mutations in BRCA1 or BRCA2: a clinic-based series. Cancer. 2005;103(1):44–51.
81. Narod SA, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet. 2000;356(9245):1876–81.
82. Gronwald J, et al. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer. 2006;118(9):2281–4.
83. Phillips KA, et al. Tamoxifen and Risk of Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. J Clin Oncol. 2013;21(35):3091–9.
84. Kauff ND, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346(21):1609–15.
85. Rebbeck TR, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346(21):1616–22.
86. Piver MS, et al. Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. A report of the Gilda Radner Familial Ovarian Cancer Registry. Cancer. 1993;71(9):2751–5.
87. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol. 2004;22(4):735–42.
88. Daly MB, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): genetic/familial high-risk assessment: breast and ovarian V.4.2013. © 2013 National Comprehensive Cancer Network, Inc. Available at NCCN.org. Accessed 4 Dec 2013.
89. Sidransky D, et al. Inherited p53 gene mutations in breast cancer. Cancer Res. 1992;52(10):2984–6.
90. Malkin D, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science. 1990;250(4985):1233–8.
91. Birch JM, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res. 1994;54(5):1298–304.
92. Srivastava S, et al. Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. Nature. 1990;348(6303):747–9.
93. Varley JM, et al. Germ-line mutations of TP53 in Li-Fraumeni families: an extended study of 39 families. Cancer Res. 1997;57(15):3245–52.
94. Li FP, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res. 1988;48(18):5358–62.
95. Gonzalez KD, et al. Beyond Li Fraumeni syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol. 2009;27(8):1250–6.
96. Nichols KE, et al. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev. 2001;10(2):83–7.
97. Hwang SJ, et al. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet. 2003;72(4):975–83.
98. Kleihues P, et al. Tumors associated with p53 germline mutations: a synopsis of 91 families. Am J Pathol. 1997;150(1):1–13.
99. Olivier M, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 2003;63(20):6643–50.
100. Birch JM, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene. 2001;20(34):4621–8.
101. Strong LC, Williams WR, Tainsky MA. The Li-Fraumeni syndrome: from clinical epidemiology to molecular genetics. Am J Epidemiol. 1992;135(2):190–9.
102. Masciari S, et al. Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. Breast Cancer Res Treat. 2012;133(3):1125–30.
103. Le Bihan C, et al. ARCAD: a method for estimating age-dependent disease risk associated with mutation carrier status from family data. Genet Epidemiol. 1995;12(1):13–25.
104. Chompret A, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer. 2000;82(12):1932–7.
105. Wu CC, et al. Joint effects of germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res. 2006;66(16):8287–92.
106. Villani A, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011;12(6):559–67.
107. Eng C. PTEN Hamartoma Tumor Syndrome (PHTS). In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews [Internet]. Seattle: University of Washington; 2001 Nov 29 [Updated 2011 Jul 21].

108. Zhou XP, et al. Germline mutations in BMPR1A/ALK3 cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan-Riley-Ruvalcaba syndromes. Am J Hum Genet. 2001;69(4):704–11.
109. Ni Y, et al. Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. Am J Hum Genet. 2008;83(2):261–8.
110. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000;37(11):828–30.
111. Pilarski R. Cowden syndrome: a critical review of the clinical literature. J Genet Couns. 2009;18(1):13–27.
112. Tan MH, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7.
113. Bubien V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet. 2013;50(4): 255–63.
114. Kutscher AH, et al. Incidence of Peutz-Jeghers syndrome. Am J Dig Dis. 1960;5:576–7.
115. Aretz S, et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat. 2005;26(6):513–9.
116. Lim W, et al. Relative frequency and morphology of cancers in STK11 mutation carriers. Gastroenterology. 2004;126(7): 1788–94.
117. Hearle N, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209–15.
118. Beggs AD, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59(7):975–86.
119. Amos CI, et al. Peutz-Jeghers syndrome. In: Pagon RA, et al., editors. GeneReviews. Seattle: University of Washington; 1993.
120. Kluijt I, et al. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. Fam Cancer. 2012;11(3): 363–9.
121. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK, editors. SEER Cancer Statistics Review, 1975–2008. Bethesda: National Cancer Institute; 2010. Posted to the SEER website 2011.
122. Kaurah P, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA. 2007;297(21): 2360–72.
123. Brooks-Wilson AR, et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. J Med Genet. 2004; 41(7):508–17.
124. Pharoah PD, et al. 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.
125. Keller G, et al. Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation. Am J Pathol. 1999;155(2):337–42.
126. Oliveira C, et al. Screening E-cadherin in gastric cancer families reveals germline mutations only in hereditary diffuse gastric cancer kindred. Hum Mutat. 2002;19(5):510–7.
127. Frebourg T, et al. Cleft lip/palate and CDH1/E-cadherin mutations in families with hereditary diffuse gastric cancer. J Med Genet. 2006;43(2):138–42.
128. Fitzgerald RC, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J Med Genet. 2010;47(7):436–44.
129. Kaurah P, Huntsman DG. Hereditary diffuse gastric cancer. In: Pagon RA, et al., editors. GeneReviews. Seattle: University of Washington; 1993.
130. Walsh T, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011;108(44): 18032–7.
131. Ripperger T, et al. Breast cancer susceptibility: current knowledge and implications for genetic counselling. Eur J Hum Genet. 2009;17(6):722–31.
132. Lalloo F, Evans DG. Familial breast cancer. Clin Genet. 2012; 82(2):105–14.
133. Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. Gynecol Oncol. 2012;124(2):347–53.
134. Shuen AY, Foulkes WD. Inherited mutations in breast cancer genes–risk and response. J Mammary Gland Biol Neoplasia. 2011;16(1):3–15.
135. Swift M, et al. Malignant neoplasms in the families of patients with ataxia-telangiectasia. Cancer Res. 1976;36(1):209–15.
136. Reiman A, et al. Lymphoid tumours and breast cancer in ataxia telangiectasia; substantial protective effect of residual ATM kinase activity against childhood tumours. Br J Cancer. 2011;105(4): 586–91.
137. Renwick A, et al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat Genet. 2006;38(8):873–5.
138. Ghimenti C, et al. Germline mutations of the BRCA1-associated ring domain (BARD1) gene in breast and breast/ovarian families negative for BRCA1 and BRCA2 alterations. Genes Chromosomes Cancer. 2002;33(3):235–42.
139. Ishitobi M, et al. Mutational analysis of BARD1 in familial breast cancer patients in Japan. Cancer Lett. 2003;200(1):1–7.
140. Ratajska M, et al. Cancer predisposing BARD1 mutations in breast-ovarian cancer families. Breast Cancer Res Treat. 2012; 131(1):89–97.
141. Bell DW, et al. Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science. 1999;286(5449):2528–31.
142. Ruijs MW, et al. The contribution of CHEK2 to the TP53-negative Li-Fraumeni phenotype. Hered Cancer Clin Pract. 2009;7(1):4.
143. Weischer M, et al. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol. 2008;26(4):542–8.
144. Adank MA, et al. CHEK2*1100delC homozygosity is associated with a high breast cancer risk in women. J Med Genet. 2011; 48(12):860–3.
145. Offit K, Garber JE. Time to check CHEK2 in families with breast cancer? J Clin Oncol. 2008;26(4):519–20.
146. Bartkova J, et al. Aberrations of the MRE11-RAD50-NBS1 DNA damage sensor complex in human breast cancer: MRE11 as a candidate familial cancer-predisposing gene. Mol Oncol. 2008;2(4):296–316.
147. Steffen J, et al. Increased cancer risk of heterozygotes with NBS1 germline mutations in Poland. Int J Cancer. 2004;111(1):67–71.
148. Buslov KG, et al. NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia. Int J Cancer. 2005;114(4):585–9.
149. Steffen J, et al. Germline mutations 657del5 of the NBS1 gene contribute significantly to the incidence of breast cancer in Central Poland. Int J Cancer. 2006;119(2):472–5.
150. Heikkinen K, et al. RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability. Carcinogenesis. 2006;27(8):1593–9.
151. Cao AY, et al. Some common mutations of RAD50 and NBS1 in western populations do not contribute significantly to Chinese non-BRCA1/2 hereditary breast cancer. Breast Cancer Res Treat. 2010;121(1):247–9.
152. He M, et al. RAD50 and NBS1 are not likely to be susceptibility genes in Chinese non-BRCA1/2 hereditary breast cancer. Breast Cancer Res Treat. 2012;133(1):111–6.
153. Tommiska J, et al. Evaluation of RAD50 in familial breast cancer predisposition. Int J Cancer. 2006;118(11):2911–6.
154. Mosor M, et al. RAD50 gene mutations are not likely a risk factor for breast cancer in Poland. Breast Cancer Res Treat. 2010;123(2): 607–9.
155. Uhrhammer N, Delort L, Bignon YJ. Rad50 c.687delT does not contribute significantly to familial breast cancer in a French

population. Cancer Epidemiol Biomarkers Prev. 2009;18(2): 684–5.
156. Solyom S, et al. Breast cancer-associated Abraxas mutation disrupts nuclear localization and DNA damage response functions. Sci Transl Med. 2012;4(122):122ra23.
157. Seal S, et al. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet. 2006;38(11):1239–41.
158. Lewis AG, et al. Mutation analysis of FANCD2, BRIP1/BACH1, LMO4 and SFN in familial breast cancer. Breast Cancer Res. 2005;7(6):R1005–16.
159. Rutter JL, et al. Mutational analysis of the BRCA1-interacting genes ZNF350/ZBRK1 and BRIP1/BACH1 among BRCA1 and BRCA2-negative probands from breast-ovarian cancer families and among early-onset breast cancer cases and reference individuals. Hum Mutat. 2003;22(2):121–8.
160. Luo L, et al. No mutations in the BACH1 gene in BRCA1 and BRCA2 negative breast-cancer families linked to 17q22. Int J Cancer. 2002;98(4):638–9.
161. McInerney NM, et al. Evaluation of variants in the CHEK2, BRIP1 and PALB2 genes in an Irish breast cancer cohort. Breast Cancer Res Treat. 2010;121(1):203–10.
162. Kuusisto KM, et al. Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. Breast Cancer Res. 2011;13(1):R20.
163. Silvestri V, et al. Mutation analysis of BRIP1 in male breast cancer cases: a population-based study in Central Italy. Breast Cancer Res Treat. 2011;126(2):539–43.
164. Solyom S, Pylkas K, Winqvist R. Screening for large genomic rearrangements of the BRIP1 and CHK1 genes in Finnish breast cancer families. Fam Cancer. 2010;9(4):537–40.
165. Ameziane N, et al. Lack of large genomic deletions in BRIP1, PALB2, and FANCD2 genes in BRCA1/2 negative familial breast cancer. Breast Cancer Res Treat. 2009;118(3):651–3.
166. Cao AY, et al. Mutation analysis of BRIP1/BACH1 in BRCA1/BRCA2 negative Chinese women with early onset breast cancer or affected relatives. Breast Cancer Res Treat. 2009;115(1): 51–5.
167. Guenard F, et al. Mutational analysis of the breast cancer susceptibility gene BRIP1/BACH1/FANCJ in high-risk non-BRCA1/BRCA2 breast cancer families. J Hum Genet. 2008; 53(7):579–91.
168. Rafnar T, et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet. 2011;43(11):1104–7.
169. Tischkowitz M, Xia B. PALB2/FANCN: recombining cancer and Fanconi anemia. Cancer Res. 2010;70(19):7353–9.
170. Rahman N, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet. 2007; 39(2):165–7.
171. Erkko H, et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature. 2007;446(7133):316–9.
172. Harinck F, et al. Routine testing for PALB2 mutations in familial pancreatic cancer families and breast cancer families with pancreatic cancer is not indicated. Eur J Hum Genet. 2012;20(5): 577–9.
173. Blanco A, et al. Detection of a large rearrangement in PALB2 in Spanish breast cancer families with male breast cancer. Breast Cancer Res Treat. 2012;132(1):307–15.
174. Hellebrand H, et al. Germline mutations in the PALB2 gene are population specific and occur with low frequencies in familial breast cancer. Hum Mutat. 2011;32(6):E2176–88.
175. Stadler ZK, et al. Germline PALB2 mutation analysis in breast-pancreas cancer families. J Med Genet. 2011;48(8):523–5.
176. Hofstatter EW, et al. PALB2 mutations in familial breast and pancreatic cancer. Fam Cancer. 2011;10(2):225–31.
177. Casadei S, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 2011;71(6):2222–9.
178. Peterlongo P, et al. PALB2 germline mutations in familial breast cancer cases with personal and family history of pancreatic cancer. Breast Cancer Res Treat. 2011;126(3):825–8.
179. Southey MC, et al. A PALB2 mutation associated with high risk of breast cancer. Breast Cancer Res. 2010;12(6):R109.
180. Bogdanova N, et al. PALB2 mutations in German and Russian patients with bilateral breast cancer. Breast Cancer Res Treat. 2011;126(2):545–50.
181. Ding YC, et al. Germline mutations in PALB2 in African-American breast cancer cases. Breast Cancer Res Treat. 2011;126(1):227–30.
182. Ding YC, et al. Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. Breast Cancer Res Treat. 2011;126(3):771–8.
183. Balia C, et al. PALB2: a novel inactivating mutation in a Italian breast cancer family. Fam Cancer. 2010;9(4):531–6.
184. Adank MA, et al. PALB2 analysis in BRCA2-like families. Breast Cancer Res Treat. 2011;127(2):357–62.
185. Kim JH, et al. PALB2 mutations 1592delT and 229delT are not present in Korean breast cancer patients negative for BRCA1 and BRCA2 mutations. Breast Cancer Res Treat. 2010;122(1):303–6.
186. Silvestri V, et al. PALB2 mutations in male breast cancer: a population-based study in Central Italy. Breast Cancer Res Treat. 2010;122(1):299–301.
187. Dansonka-Mieszkowska A, et al. A novel germline PALB2 deletion in Polish breast and ovarian cancer patients. BMC Med Genet. 2010;11:20.
188. Ghadirian P, et al. The contribution of founder mutations to early-onset breast cancer in French-Canadian women. Clin Genet. 2009;76(5):421–6.
189. Papi L, et al. A PALB2 germline mutation associated with hereditary breast cancer in Italy. Fam Cancer. 2010;9(2):181–5.
190. Heikkinen T, et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res. 2009;15(9):3214–22.
191. Sluiter M, Mew S, van Rensburg EJ. PALB2 sequence variants in young South African breast cancer patients. Fam Cancer. 2009; 8(4):347–53.
192. Gunnarsson H, et al. Evidence against PALB2 involvement in Icelandic breast cancer susceptibility. J Negat Results Biomed. 2008;7:5.
193. Pylkas K, et al. Analysis of large deletions in BRCA1, BRCA2 and PALB2 genes in Finnish breast and ovarian cancer families. BMC Cancer. 2008;8:146.
194. Cao AY, et al. The prevalence of PALB2 germline mutations in BRCA1/BRCA2 negative Chinese women with early onset breast cancer or affected relatives. Breast Cancer Res Treat. 2009;114(3): 457–62.
195. Garcia MJ, et al. Analysis of FANCB and FANCN/PALB2 fanconi anemia genes in BRCA1/2-negative Spanish breast cancer families. Breast Cancer Res Treat. 2009;113(3):545–51.
196. Foulkes WD, et al. Identification of a novel truncating PALB2 mutation and analysis of its contribution to early-onset breast cancer in French-Canadian women. Breast Cancer Res. 2007;9(6):R83.
197. Tischkowitz M, et al. Analysis of PALB2/FANCN-associated breast cancer families. Proc Natl Acad Sci U S A. 2007;104(16): 6788–93.
198. Erkko H, et al. Penetrance analysis of the PALB2 c.1592delT founder mutation. Clin Cancer Res. 2008;14(14):4667–71.
199. Krejci L, et al. Homologous recombination and its regulation. Nucleic Acids Res. 2012;40(13):5795–818.
200. Suwaki N, Klare K, Tarsounas M. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. Semin Cell Dev Biol. 2011;22(8):898–905.

201. Vaz F, et al. Mutation of the RAD51C gene in a Fanconi anemia-like disorder. Nat Genet. 2010;42(5):406–9.
202. Thompson ER, et al. Analysis of RAD51C germline mutations in high-risk breast and ovarian cancer families and ovarian cancer patients. Hum Mutat. 2012;33(1):95–9.
203. Vuorela M, et al. Further evidence for the contribution of the RAD51C gene in hereditary breast and ovarian cancer susceptibility. Breast Cancer Res Treat. 2011;130(3):1003–10.
204. Romero A, et al. A HRM-based screening method detects RAD51C germ-line deleterious mutations in Spanish breast and ovarian cancer families. Breast Cancer Res Treat. 2011;129(3):939–46.
205. Wickramanyake A, et al. Loss of function germline mutations in RAD51D in women with ovarian carcinoma. Gynecol Oncol. 2012;127(3):552–5.
206. Coulet F, et al. Germline RAD51C mutations in ovarian cancer susceptibility. Clin Genet. 2013;83(4):332–6.
207. Pelttari LM, et al. RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet. 2011;20(16):3278–88.
208. Park DJ, et al. Rare mutations in XRCC2 increase the risk of breast cancer. Am J Hum Genet. 2012;90(4):734–9.
209. Hilbers FS, et al. Rare variants in XRCC2 as breast cancer susceptibility alleles. J Med Genet. 2012;49(10):618–20.
210. Lee SA, et al. Genetic polymorphism of XRCC3 Thr241Met and breast cancer risk: case-control study in Korean women and meta-analysis of 12 studies. Breast Cancer Res Treat. 2007;103(1):71–6.
211. Zhang B, et al. Genetic variants associated with breast-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. Lancet Oncol. 2011;12(5):477–88.
212. Orr N, et al. Genome-wide association study identifies a common variant in RAD51B associated with male breast cancer risk. Nat Genet. 2012;44(11):1182–4.
213. Johnson J, et al. Mutation analysis of RAD51L1 (RAD51B/REC2) in multiple-case, non-BRCA1/2 breast cancer families. Breast Cancer Res Treat. 2011;129(1):255–63.
214. Weissman SM, et al. Genetic counseling considerations in the evaluation of families for Lynch syndrome–a review. J Genet Couns. 2011;20(1):5–19.
215. Watson P, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer. 2008;123(2):444–9.
216. Win AK, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol. 2012;30(9):958–64.
217. Walsh MD, et al. Lynch syndrome-associated breast cancers: clinicopathologic characteristics of a case series from the colon cancer family registry. Clin Cancer Res. 2010;16(7):2214–24.
218. Buerki N, et al. Evidence for breast cancer as an integral part of Lynch syndrome. Genes Chromosomes Cancer. 2012;51(1):83–91.
219. Lefevre JH, et al. MYH biallelic mutation can inactivate the two genetic pathways of colorectal cancer by APC or MLH1 transversions. Fam Cancer. 2010;9(4):589–94.
220. Sieber OM, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med. 2003;348(9):791–9.
221. Boparai KS, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology. 2008;135(6):2014–8.
222. Vogt S, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology. 2009;137(6):1976–85 e1-10.
223. Nielsen M, et al. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). J Med Genet. 2005;42(9):e54.
224. Beiner ME, et al. Mutations of the MYH gene do not substantially contribute to the risk of breast cancer. Breast Cancer Res Treat. 2009;114(3):575–8.
225. Lowry KP, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer. 2012;118:2021–30.