# Genetic Evaluation for Women at Increased Risk

2

Karina L. Brierley, Claire L. Healy and Erin W. Hofstatter

## Hereditary Cancer Risk Assessment

The US Preventative Services Task Force recommends providers perform a risk assessment in order to identify those who have a personal and/or family history of cancer that may be associated with a hereditary cancer predisposition. The collection of an accurate, cancer-focused family history is the foundation of this risk assessment [1–3].

## What to Collect

Several physician organizations, including the American Society of Clinical Oncology (ASCO), have developed standards for the minimum collection requirements for an adequate family history. At a minimum, these include the following [4]:

K.L. Brierley · C.L. Healy
Smilow Cancer Genetics and Prevention Program, Yale New Haven Hospital,
330 Orchard Street, New Haven, CT 06511, USA
e-mail: karina.brierley@ynhh.org

C.L. Healy
e-mail: claire.healy@ynhh.org

E.W. Hofstatter (✉)
Department of Medical Oncology, Smilow Cancer Genetics
and Prevention Program, Yale New Haven Hospital/Yale School of Medicine,
333 Cedar Street, New Haven, CT 06520, USA
e-mail: erin.hofstatter@yale.edu



A.B. Chagpar (ed.), *Managing BRCA Mutation Carriers*,
DOI 10.1007/978-3-319-59198-8_2

1. Personal cancer history;
2. Cancer history of first degree relatives, i.e., siblings, parents, and children;
3. Cancer history of second degree relatives, i.e., grandparents, aunts, uncles, grandchildren, nieces, nephews, and half-siblings;
4. Inclusion of relatives on both the maternal and paternal side; and
5. Inclusion of information on the patient's ethnicity.

For each individual in the family where a cancer diagnosis is reported by the patient, it is important to collect the following information [4]:

1. Type of primary cancer;
2. Age at diagnosis of each primary cancer; and
3. Lineage (i.e., is the family member a maternal or paternal relative).

While not included in the minimum collection requirements, providers should consider asking whether there is a known hereditary cancer predisposition syndrome in the family and whether any family members have had genetic testing [4].

An accurate risk assessment is also dependent on family size. It is often just as important to know how many unaffected relatives there are in the family as there are individuals with cancer. For example, the risk for a hereditary cancer syndrome in an individual with a mother and aunt with breast cancer is substantially lower if the mother also had five sisters who have not developed cancer [1].

## When to Collect

Cancer family history is typically collected at the initial visit and/or at the time of a patient's cancer diagnosis. However, after a patient has been diagnosed with cancer and has shared the diagnosis with other family members, conversations regarding the family history of cancer may occur which may alter the patient's initial report. Relatives may be more likely to share stories of other family members who have had cancer after learning of a recent diagnosis. For this reason, providers should consider reassessing the family history after the initial stress of a cancer diagnosis has abated [1].

It is also important to periodically reassess the family history, as cancer history can change significantly over time. Reassessment should include elicitation of any new family history information, as well as a determination of whether advances in genetic testing technology or the discovery of additional genes linked to hereditary cancer predispositions have occurred since the last evaluation, which may require re-referral and/or updated testing [4].

## How to Collect

With limited time available, providers may struggle with how to collect adequate family history information. Some providers prefer to utilize a patient-centered collection tool prior to the visit. Patients can complete these questionnaires in the waiting room or at home prior to seeing their provider, and the collected information can then be reviewed and expanded upon in the visit. There are a number of organizations that have developed patient-friendly questionnaires for this purpose, including the following:

1. Cancer.Net Cancer Family History Questionnaire which is based on ASCO's recommendations for a minimum adequate family history [5]: http://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf
2. The US Surgeon General's My Family Health Portrait tool which can be accessed online or printed out and given to patients [6]: http://www.hhs.gov/programs/prevention-and-wellness/family-health-history/family-health-portrait-tool/index.html#

Regardless of whether the provider is reviewing information, the patient has provided through a questionnaire, or whether they are starting the family history collection from scratch, setting expectations with the patient prior to collecting or reviewing the information can be helpful in streamlining the intake of information [1]. Patients are more likely to provide concise responses if they know what information the provider is looking for ahead of time.

## Limitations

There can be a number of barriers to obtaining an accurate and useful hereditary cancer risk assessment.

1. ***Patient Barriers***

Patients may have limited or no knowledge of their family history due to:

(a) Adoption or conception through donor eggs/sperm;
(b) Family estrangement; and
(c) Cultural barriers that prevent the discussion of cancer diagnoses.

In these situations, providers should focus on the information that is available while making note of the barriers that limit the risk assessment [1].

2. ***Provider Barriers***

Obtaining an accurate family history and determining who would benefit from additional risk assessment and genetic testing can be time consuming. In a world

where providers are asked to do more with less time, it may be challenging to collect the necessary information. Utilizing patient questionnaires and tools like the ones mentioned above may help to reduce the amount of time providers spend on this task [4].

## Guidelines for Further Risk Assessment and Genetic Testing

Many professional organizations have created guidelines outlining when patients should be referred to a provider with expertise in hereditary cancer genetics for further risk assessment, as well as when genetic testing should be performed. It is important to note that the criteria for further risk assessment are not identical to the criteria for genetic testing. Some patients who are referred for further risk assessment may not meet guidelines for genetic testing but may still be candidates for increased screening, behavior modifications, or medical interventions due to their personal and/or family history [2].

In some instances, the a priori risk for a mutation will be high enough based on a patient's personal history such that no further family history is needed to warrant further risk evaluation. This can include the following [7]:

1. Any individual with or without a cancer diagnosis who has a known mutation in a cancer susceptibility gene within their family;
2. Any man with a diagnosis of breast cancer;
3. Any woman with ovarian cancer;
4. Any woman with breast cancer diagnosed $\leq 45$ years old; and/or
5. Any woman with a triple negative breast cancer diagnosed $\leq 60$ years old.

Individuals of Ashkenazi Jewish descent also have a higher a priori risk due to the increased frequency of founder mutations in the *BRCA1* and *BRCA2* genes among this population. Approximately, 1 in 40 (2.5%) of individuals of Ashkenazi Jewish descent will carry a mutation in *BRCA1* or *BRCA2* versus the approximate carrier frequency of 1 in 400 (0.25%) in the Western European population [3]. Due to this increased frequency of mutations within this population, it is recommended that any individual of Ashkenazi Jewish descent with a diagnosis of breast, ovarian, or pancreatic cancer, regardless of age or family history, be referred for further risk assessment [7].

Oftentimes, the decision to refer a patient for further risk evaluation is based on a combination of personal and/or family history information. However, it is difficult to convey the myriad possible combinations of personal and family history of cancer that should prompt a referral to a specialist in cancer genetics for further risk evaluation. Table 2.1 lists common scenarios for which providers should pursue referral for risk assessment [7]. Providers may also wish to familiarize themselves with and utilize the 2015 practice guidelines published by the American College of

**Table 2.1** Common scenarios for which providers should pursue referral for risk assessment [7]

| **Individuals with a personal history of breast cancer at any age plus any of the following in a first, second, or third degree relative:** | **Individuals without a personal diagnosis of cancer who have a family history of the following in a first, second, or third degree relative:** |
|---|---|
| At least one relative with breast cancer diagnosed $\leq$ 50 years old | $\geq$ Two breast cancers in a single relative |
| At least one relative with invasive ovarian cancer at any age | $\geq$ Two relatives with breast cancer at least one of whom was diagnosed $\leq$ 50 years old |
| $\geq$ Two relatives with breast cancer at any age | A relative with ovarian cancer |
| $\geq$ Two relatives with pancreatic cancer at any age | A relative with male breast cancer |

Medical Genetics & Genomics and the National Society of Genetic Counselors [8]. This document was created in an easy-to-read table and is designed to allow providers to cross-reference a specific type of cancer against the family history necessary to warrant referral.

## Provision of Cancer Genetic Counseling and Testing

Over the past 20 years, the field of cancer genetic counseling and testing has grown exponentially and changed rapidly. Throughout its growth and evolution, there has been debate about which health care providers should provide these services, namely, only genetics specialists versus all health care providers regardless of specialty [9, 10]. Recent decisions by several large insurers to require genetic counseling by a certified genetics provider prior to cancer genetic testing, as well as the increasing complexity of the available cancer genetic testing options, have sparked renewed interest in this debate.

Some argue that all health care providers should provide genetic counseling and testing services based on the potential benefits of increased access to genetic services, cost efficiency, a more holistic approach, and better knowledge of patients' overall health due to existing long-term relationships [10]. On the other hand, there is much literature and expert opinion to support the belief that cancer genetic counseling and testing should ideally be provided by genetics specialists [9]. Specifically, numerous studies have demonstrated that many providers lack the training in and knowledge of genetics to adequately provide cancer genetic counseling and testing services to their patients [9, 11–13]. This includes data even on those providers who arguably have the most current genetics education and training, such as medical residents, and includes key concepts such as associated cancer risks and inheritance patterns [12]. Many providers also self-report lack of adequate time as a barrier to providing cancer genetic counseling and testing services [9, 11]. In addition, existing data suggest that many providers are not sufficiently familiar

with the complex ethical and psychosocial issues that often accompany genetic counseling and testing, such as genetic discrimination concerns and the existing laws, concerns and policies regarding testing minors for adult-onset conditions [9, 14–16].

Although the availability of cancer genetics professionals is increasing and access to cancer genetics professionals is readily available in many areas, there may still be locations where these services are not as readily available. In locations where geography presents concerns regarding adequate access to genetics professionals, telemedicine genetic counseling services with board certified professionals are now available and covered by several major insurers. Recent studies suggest that telemedicine genetic counseling is cost-effective, associated with high patient satisfaction, and is equally effective as in-person genetic counseling [17, 18]. Ultimately, multidisciplinary teams, increased genetics education for all providers, self-awareness, close collaborations, and open lines of communication and referral will likely best serve patients and providers alike. Table 2.2 lists information about locating in-person- and/or telemedicine-based cancer genetic counseling professional services [19–22].

## Cancer Genetic Counseling and Testing Process

Cancer genetic counseling has been described as a multistep communication process between a clinician and a patient/family of which the actual genetic testing is only one component [23]. For some individuals, this process occurs even without actual

**Table 2.2** Resources for locating a genetic counselor [19–22]

| |
|---|
| **National Society of Genetic Counselors (NSGC)** [19]<br>http://nsgc.org/page/find-a-gc-search<br>Database of genetic counselors who are members of the NSGC that is searchable by geographic location and specialty |
| **National Cancer Institute (NCI) Cancer Genetics Services Directory** [20]<br>https://www.cancer.gov/about-cancer/causes-prevention/genetics/directory<br>Directory of professionals who provide services related to cancer genetics (including genetic counselors) |
| **Informed DNA** [21]<br>http://www.informeddna.com/<br>Nationwide network of genetic counselors that provides telephone and Web-based genetic counseling services to patients and providers that are covered by some major insurers |
| **GeneTests** [22]<br>https://www.genetests.org/<br>Gene Tests has an international directory of genetics professionals searchable by location, role, and specialty as well as an international directory of genetics clinics searchable by location and keywords |

genetic testing as it may be determined that testing is not warranted, the patient is not the best candidate for testing in their family, and/or the patient is not interested in pursuing testing. Some of the essential elements in the cancer genetic counseling and testing process include the following: intake, risk assessment, pretest counseling and informed consent, and result disclosure and interpretation [24].

The intake/history component of the genetic counseling process should include collection of a detailed personal medical history and a 3–4 generation family history in order to provide accurate risk assessment, differential diagnosis, and development of a personalized management plan. The intake should also include an assessment of the patient's concerns, motivations, needs, values, and knowledge or understanding of the pertinent information related to cancer genetics [23, 24]. The personal history should include any diagnoses of cancer, benign tumors, or unusual findings that may be relevant to risk assessment (e.g., multiple colon polyps, skin findings), frequency of cancer surveillance, surgical interventions, environmental exposures (e.g., tobacco use, occupational exposures), and reproductive information (e.g., oral contraceptive use, tubal ligation) [24]. An accurate family history is an essential tool in the hereditary cancer risk assessment and result interpretation. The 3–4 generation family history should include information on both affected and unaffected individuals, their relationship to the patient, current age or age at death, the site and age at diagnosis for any cancer diagnoses, ancestry/ethnicity, consanguinity, surgical interventions (which may reduce the cancer incidence), any findings that may be relevant to differential diagnoses under consideration (e.g., multiple polyps, unusual skin findings, autism spectrum disorders, benign tumors), and the results of any prior genetic testing on family members [24]. Information about family history may be inaccurate and thus, efforts should be made to confirm family history information with medical records or death certificates when possible to improve accuracy of risk assessment [24]. Interestingly, cancer type, gender of historian, education level, family size, and degree of relatedness to affected relative have all been shown to impact the accuracy of reporting of cancer diagnoses among relatives [25]. Reporting of results of prior genetic testing on relatives is also often inaccurate or incomplete and thus should also be confirmed with records.

Based on the personal and family history information collected, a risk assessment and differential diagnosis should be generated. In general, the risk assessment should distinguish between individuals at: high risk (personal and/or family history consistent with a highly penetrant hereditary cancer syndrome), moderately increased risk (history consistent with either a multifactorial cause or a low- to moderate-penetrance mutation), and average risk [23, 24]. The risk assessment, differential diagnosis, ideal testing strategy, and available testing options should be discussed with the patient.

## Whom to Test

In order to obtain the most accurate interpretation of genetic test results, it is preferable to start genetic testing with an individual in the family who is most likely

to carry a mutation. This may not always be the individual who presents for the initial risk assessment. Beginning genetic testing in an individual who has had a cancer diagnosis most closely related to the hereditary cancer syndrome in question (i.e., breast or ovarian cancer in *BRCA1* and *BRCA2*) is likely to yield the most informative results for the family. If there are multiple relatives in a family with an associated cancer diagnosis who are available for testing, priority could be given to those with bilateral disease, multiple primary cancers, or the youngest age at diagnosis [25].

In some instances, there will not be an affected individual available for testing, or the results of an affected relatives genetic testing may be inaccessible, due to death, estrangement, or a refusal to pursue testing. In these situations, testing an individual without a cancer diagnosis may be appropriate but the limitations of a negative genetic test result should be clearly reviewed.

When there is significant suspicion for a hereditary cancer predisposition in a family, a negative genetic test results in an unaffected individual could be explained in two ways:

1. There is a mutation in a hereditary cancer gene in the family which the patient did not inherit. In this instance, the patient's risk to develop cancer would be the same as an individual in the general population; or,
2. There is no currently identifiable mutation in a hereditary cancer gene in the family. In this instance, the patient's risk to develop cancer would still be considered elevated above the general population risk, and screening and prevention decisions would be based on the family history.

Given that it is not possible to distinguish between these two explanations when the only genetic testing that has been completed in a family was in an individual without a cancer diagnosis, providers should err on the side of caution and follow their patients based on family history despite their negative genetic test results.

In general, a detailed informed consent process should accompany any genetic testing and in some states informed consent is required by law [24]. The informed consent process should include a discussion of the genes being testing, the possible test results [positive, negative, variant of uncertain significance (VUS)], how results may impact the individual's cancer risks and medical management options, how results may impact family members' risks, ethical/legal/psychosocial aspects (e.g., discrimination issues and protections, family issues), economic considerations (e.g., potential costs and coverage), and a review of the benefits, risks, limitations, and alternatives to genetic testing [24]. For patients who choose not to proceed with testing, recommendations for cancer screening, and prevention based on personal and family history alone should be reviewed as well as recommendations for genetic counseling and testing for other relatives, if applicable [24].

Disclosure of the results of any genetic testing, regardless of the test result (positive, negative, or VUS), should be accompanied by a thorough discussion including the following: a personalized interpretation of the results in the context of the individual's personal and family history, revised cancer risk assessment,

medical management guidelines/recommendations, identification of at-risk relatives and/or other relatives who may benefit from genetic counseling and testing, and tools to assist the patient in informing family members (e.g., family letter, online resources, referrals to genetics providers) [24].

## Hereditary Breast and Ovarian Cancer Testing Options

The intersection of the introduction of mainstream use of next-generation sequencing technology and the Supreme Court ruling overturning gene patenting in 2013 has led to exponential growth of the available testing options and laboratory choices for hereditary breast cancer testing [26, 27]. In addition, these developments have also led to increased availability of low-cost testing options, with out-of-pocket costs ranging in several hundred dollars, rather than several thousand dollars. There are now more than 10 laboratories offering *BRCA1* and *BRCA2* testing as a targeted test or as part of one of the dozens of multi-gene panel test options, ranging from 6 to 100+ genes. These developments mean that broader genetic testing options for *BRCA1* and *BRCA2* and other hereditary cancer genes are available to clinicians and patients, and that testing is likely to be accessible and affordable for more patients even if they lack insurance coverage for testing. However, it also means that navigating the available choices can be complicated, particularly in the context of aggressive marketing efforts by the commercial testing laboratories who are trying to secure business in a competitive marketplace. In the face of this multitude of laboratory and testing choices, there are a number of aspects to consider when choosing a laboratory and test. These include quality, methods, data sharing, cost, insurance verification process, genes included in available panels, variant classification, variant analysis and reporting process, and family studies programs for variants [28, 29].

Multi-gene panel tests offer the advantage of cost- and time-efficient testing for multiple genes. Several studies have now demonstrated that multi-gene panel testing does provide additional diagnostic yield compared to a syndrome-specific gene testing approach, with an absolute additional yield of identification of a deleterious mutation in ~4–16% of individuals, meaning that this approach to testing may identify the causative mutation in additional individuals/families [26, 30, 31]. At least one of these studies also demonstrated that this additional yield of mutations changed the management for the patient and/or close relatives in many cases [31]. However, the benefits of multi-gene panel testing over syndrome-specific gene testing must be balanced by the limitations, particularly several layers of complexity and uncertainty that can come with this testing [26, 29]. One important layer of complexity is that multi-gene panel testing is currently associated with a high rate of identification of variants of uncertain significance, ranging from 28 to 40% [27, 30, 31]. These variants often can be misinterpreted by

providers and patients as clinically relevant (i.e., potentially associated with high cancer risks), when typically these variants are later reclassified as normal, benign variants [29, 32]. Thus, this can be an important source of unnecessary worry, anxiety, and, most critically, unnecessary medical interventions, including invasive "prophylactic" surgeries [29, 32].

Another layer of uncertainty that arises frequently with the advent of multi-gene panel testing is the identification of deleterious mutations in genes where the clinical implications are less clear [29]. Many gene panels include more newly described, "moderate-penetrance" genes for which data are often more limited regarding the exact cancer risks, range of associated cancers, and appropriate management recommendations [29]. Thus, determining how to use this information can be challenging for patients and providers alike. Identification of a mutation in a more newly described or lower penetrance gene may also pose other result interpretation and/or medical management challenges for providers, patients, and family members as it is not always clear if the identified mutation completely explains the personal and/or family history that prompted testing. This leads to difficulties in making decisions about whether or not to test other relatives, interpreting "true negative" test results, and determining residual risks and appropriate management [26].

An additional challenge posed by multi-gene panel testing is the possibility of an unexpected mutation in high-penetrance gene that is not consistent with the known history that prompted testing [26]. These unexpected results again can be challenging to interpret in terms of advising patients and their family members regarding expected cancer risks and appropriate management, as there is very little data at this time regarding whether the presentation, severity, and risks will be different in families where mutation is an "incidental finding" and thus, whether management should be based on genotype alone, phenotype alone, or some combination of the two.

A sometimes less recognized or appreciated but important challenge of current cancer genetic testing choices is that the classification of a given variant can differ from one laboratory to the next, with different laboratories classifying the same genetic change or variant as a variant of uncertain significance, a likely pathogenic variant, or a pathogenic variant (mutation) [27]. These discrepancies can occur based on conflicting interpretations of available data.

For all of these reasons, testing should be ideally offered in the context of care by professionals with genetics expertise [26, 27, 29, 33]. In addition, determination of the most appropriate testing options should be made by the clinician based on the patient's clinical and family history. When a choice between more limited syndrome-specific testing and broader multi-gene panel testing is reasonable, the clinician should help the patient make an informed choice based on a discussion of the benefits and limitations of the available options and the patient's values and preferences [29].

## Hereditary Breast and/or Ovarian Cancer Genes Frequently Included in Multi-gene Panels

The focus of this volume is the management of individuals with *BRCA* mutations, as *BRCA1* and *BRCA2* are the most common genes associated with hereditary breast and/or ovarian cancer. However, any current discussion of hereditary breast and ovarian cancer would not be complete without mention of other rare high-penetrance genes and moderate-penetrance genes that are now included in many routine clinical genetic testing options for hereditary breast and ovarian cancer. In addition to *BRCA1* and *BRCA2*, there are several rare hereditary cancer syndromes that place individuals at high risk of developing breast cancer including the following: Li-Fraumeni Syndrome, Cowden Syndrome, Peutz-Jeghers Syndrome, and hereditary diffuse gastric cancer.

***Li-Fraumeni Syndrome (LFS)*** is caused by mutations in the *TP53* gene and is associated with a diverse range of cancers [34]. The lifetime risk of developing cancer with a *TP53* mutation is ~90% and individuals are at high risk to develop multiple primary cancers [34, 35]. The core cancers associated with LFS are soft tissue sarcomas, osteosarcomas, brain tumors, very early-onset breast cancer, and adrenal cortical carcinoma. However, individuals with LFS can develop a wide range of cancers. LFS is a rare hereditary cancer syndrome with an estimated prevalence of ~1/5000–1/20,000 and accounts for ~1% or less of breast cancer cases [34, 35]. However, breast cancer is the most frequent cancer among female carriers of *TP53* mutations and in many cases breast cancer occurs before age 30 [34].

***Cowden Syndrome*** is a rare hereditary cancer syndrome (prevalence of ~1/200,000–1/250,000) caused by mutations in the *PTEN* gene [33, 36]. *PTEN* hamartoma tumor syndrome refers to a broader range of syndromes, including Cowden Syndrome and Bananayan-Riley-Ruvalcaba syndrome, that can be associated with *PTEN* mutations. Cowden Syndrome/*PTEN* hamartoma tumor syndrome is associated with multiple hamartomas and a high risk of benign and cancerous tumors in a variety of tissues including the breast, thyroid, and endometrium [35, 36]. The lifetime risk of breast cancer associated with *PTEN* mutations is ~25–50% by most estimates, although a few studies report higher risks, as high as ~75–85% [36, 37]. *PTEN* hamartoma tumor syndrome is also associated with a wide range of features including unusual mucocutaneous features (oral papillomas, trichilemmomas, penile freckling), macrocephaly, developmental delay, autism spectrum disorders, multiple gastrointestinal polyps (including hamartomas and ganglioneuromas), and vascular malformations [36, 38].

***Peutz-Jeghers Syndrome (PJS)*** is caused by mutations in the *STK11* (or *LKB1*) gene and is a rare autosomal dominant hereditary cancer syndrome (prevalence estimates of ~1/25,000–1/280,000) [39]. PJS is associated with mucocutaneous hyperpigmentation (melanocytic macules on buccal mucosa, lips, nostrils, fingers) and multiple hamartomatous gastrointestinal polyps (especially in the small intestine) often resulting in symptoms (e.g., intussusception, obstruction, gastrointestinal

bleeding) [39]. The lifetime cancer risk associated with PJS is ~50–85%, with the highest risks being for colorectal and breast cancers, but risks for stomach, small intestine, pancreatic, gynecologic, testicular, and lung cancers are also increased [39, 40]. Women with PJS have a lifetime risk of breast cancer of ~32–54% and are at increased risk for ovarian sex cord tumors with annular tubules (SCTATs) and adenoma malignum of the cervix [33, 39].

***Hereditary diffuse gastric cancer*** is associated with mutations in the E-cadherin (*CDH1*) gene. Individuals with a germline *CDH1* mutation have a ~65–85% lifetime risk of developing diffuse gastric cancer with an average age of diagnosis of 40 years old [35, 41, 42]. Women who carry a *CDH1* mutation have a ~40–54% lifetime risk of developing breast cancer, primarily of the lobular subtype [35, 41, 42]. Mutations in the *CDH1* gene are thought to be rare with prevalence of <0.1/100,000.

Over recent years, other genes associated with hereditary breast and/or ovarian cancer, most of which are currently considered "moderate-penetrance" genes, have been identified and are now included on many multi-gene hereditary cancer testing panels. The distinction between "moderate" and "high" risk is somewhat arbitrary as the lifetime risk ranges for several "moderate" risk genes overlap with "high" risk genes [43]. However, current data suggest that the risks associated with some of these genes may vary significantly based on specific mutation and/or family history [43]. These "moderate-penetrance" genes have mainly been identified by searching for mutations in genes that share some functionality with *BRCA1* and *BRCA2* either by directly interacting with the *BRCA* proteins and/or being involved in the Fanconi anemia pathway which is involved in double strand DNA break repair and homologous recombination. Their association with hereditary breast and/or ovarian cancers has been strengthened by the identification of mutations in these genes in individuals and/or families whose history was suspicious for hereditary breast and/or ovarian cancer and had negative *BRCA1/2* testing. These genes and current information about the associated cancer risks are listed in Table 2.3 [27, 34–50].

**Table 2.3** Associated cancer risks of high- and moderate-penetrance genes [27, 34–50]

| Gene(s) | Breast cancer lifetime risk | Ovarian cancer lifetime risk | Other associated cancers/features |
|---|---|---|---|
| **High-penetrance genes** | | | |
| *BRCA1* | 55–87% | 15–60% | Prostate |
| | | | Male breast |
| | | | Pancreas |
| *BRCA2* | 45–82% | 15–40% | Prostate |
| | | | Male breast |
| | | | Pancreas |
| | | | Melanoma |

(continued)

**Table 2.3** (continued)

| Gene(s) | Breast cancer lifetime risk | Ovarian cancer lifetime risk | Other associated cancers/features |
|---|---|---|---|
| *CDH1* | 39–53% (particularly lobular) | No known increase | Diffuse gastric (55–85%) |
| | | | Possibly colon |
| *PTEN* | ~25–50% by most estimates (some higher estimates) | No known increase | Thyroid, endometrial, renal, and possibly colorectal cancer |
| | | | Benign breast and thyroid disease |
| | | | Uterine fibroid tumors |
| | | | Skin findings (oral papillomas, facial trichilemmomas) |
| | | | Macrocephaly |
| | | | Developmental delay |
| | | | Autism spectrum disorders |
| | | | Multiple GI polyps (including hamartomas and ganglioneuromas) |
| | | | Vascular malformations |
| *STK11* | 32–54% | 18–21% (mainly sex cord stromal) | Colorectal, gastric, pancreatic, uterine, small intestine, testicular, and lung cancers |
| | | | Multiple hamartomatous GI polyps mucocutaneous hyperpigmentation |
| *TP53* | Significantly increased, may be as high as 79% | Unknown/not well defined | Sarcoma, brain, adrenal cortical carcinoma, leukemia, lung, and other cancers |
| | | | Childhood onset cancers |
| | | | Multiple primary cancers |
| **Moderate-penetrance genes** | | | |
| *ATM* | 17–52% | No known increase | Possibly pancreas and prostate, but limited data |
| *BARD1* | Increased | Unknown/ insufficient data | None known |
| *BRIP1* | Possibly increased/ insufficient and conflicting data | Increased (up to ~10–13%) | None known |
| *CHEK2* | 18–40% | No known increase | Possibly colon, melanoma, male breast, and others (prostate, kidney, thyroid) |
| *MRE11A* | Possibly increased/ insufficient data | Unknown/ insufficient data | None known |
| *NBN* | Increased (may be as high as ~30%) | No known increase | None known |

(continued)

**Table 2.3** (continued)

| Gene(s) | Breast cancer lifetime risk | Ovarian cancer lifetime risk | Other associated cancers/features |
|---|---|---|---|
| *NF1* | Increased/not well defined (may be as high as ~26%) | No known increase | Neurofibromas |
| | | | Multiple café-au-lait spots |
| | | | Axillary and inguinal freckling |
| | | | Optic nerve and CNS gliomas |
| | | | Malignant peripheral nerve sheath tumors |
| | | | GIST |
| *PALB2* | 30–58% | Unknown/insufficient data | Possibly pancreas and male breast |
| *RAD50* | Possibly increased/ insufficient data | Unknown/insufficient data | None known |
| *RAD51C* | Unknown/insufficient data | Increased/not well defined (may be ~6–7%) | None known |
| *RAD51D* | Unknown/insufficient data | Increased/not well defined (may be ~7–14%) | None known |

## References


1. Schneider K. Counseling about cancer: strategies for genetic counseling. 3rd ed. Hoboken: Wiley-Blackwell; 2012.
2. The American College of Obstetricians and Gynecologists (ACOG) Committee on Genetics. Hereditary cancer syndromes and risk assessment. Obstetr Gynecol. 2015;125:1538–43.
3. U.S. Preventative Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: recommendation statement. Am Fam Physician. 2015;91:118A–E.
4. Lu KH, Wood ME, Daniels M, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. J Clin Oncol. 2014;32:833–40.
5. Cancer.Net Family History Questionnaire, last accessed 10/2016: http://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf.
6. US Surgeon General My Family Health Portrait Tool, last accessed 10/2016: http://www.hhs.gov/programs/prevention-and-wellness/family-health-history/family-health-portrait-tool/index.html#.
7. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2017. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed October 7, 2016.
8. Hampel H, Bennett R, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2014;17:70–87.
9. Greendale K, Pyeritz RE. Empowering primary care health professionals in medical genetics: How soon? How fast? How far? Am J Med Genet. 2001;106:223–32.
10. Guttmacher AE, Jenkins J, Uhlmann WR. Genomic medicine: Who will practice it? A call to open arms. Am J Med Genet. 2001;106:216–22.

11. Suther S, Goodson P. Barriers to the provision of genetic services by primary care physicians: a systematic review of the literature. Genet Med. 2003;5(2):70–6.
12. Ready KJ, Daniels MS, Sun CC, et al. Obstetrics/Gynecology residents' knowledge of hereditary breast and ovarian cancer and Lynch syndrome. J Cancer Educ. 2010;25:401–4.
13. Wideroff L, Vadaparampil ST, Greene MH, et al. Hereditary breast/ovarian and colorectal cancer genetics knowledge in a national sample of US physicians. J Med Genet. 2005;42:749–55.
14. Lowstuter KJ, Sand S, Blazer KR, et al. Influence of genetic discrimination perceptions and knowledge on cancer genetics referral practice among clinicians. Genet Med. 2008;10 (9):691–8.
15. O'Neill SC, Peshkin BN, Luta G, et al. Primary care providers' willingness to recommend BRCA1/2 testing to adolescents. Fam Cancer. 2010;9:43–50.
16. Laedtke AL, O'Neill SM, Rubinstein WS, Vogel KJ. Family physicians' awareness and knowledge of the Genetic Information Non-Discrimination Act (GINA). J Genet Counsel. 2012;21(2):345–52.
17. Platten U, Rantala J, Lindblom A, et al. The use of telephone in genetic counseling versus in-person counseling: a randomized study on counselees' outcome. Fam Cancer. 2012;11 (3):371.
18. Buchanan AH, Datta SK, Skinner CS, et al. Randomized trial of telegenetics vs. in-person cancer genetic counseling: cost, patient satisfaction and attendance. J Genet Counsel. 2015;24:961–970.
19. National Society of Genetic Counselors website, last accessed 10/2016: http://nsgc.org.
20. National Cancer Institute website, last accessed 10/2016: https://www.cancer.gov.
21. Informed DNA website, last accessed 10/2016: http://www.informeddna.com.
22. GeneTests website, last accessed 10/2016: https://www.genetests.org.
23. Christinat A, Pagani O. Practical aspects of genetic counseling in breast cancer: lights and shadows. Breast. 2013;22:375–82.
24. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. J Genet Counsel. 2012;21:151–61.
25. Schneider KA, DiGianni LM, Patenaude AF, et al. Accuracy of cancer family histories: comparison of two breast cancer syndromes. Genet Test. 2004;8(3):222–8.
26. Kurian AW, Kingham KE, Ford JM. Next-generation sequencing for hereditary breast and gynecologic cancer risk assessment. Curr Opin Obstet Gynecol. 2015;27(1):23–33.
27. Hall MJ, Obeid EI, Schwartz SC, et al. Genetic testing for hereditary cancer predisposition: BRCA1/2, Lynch syndrome, and beyond. Gynecol Oncol. 2016;140:565–74.
28. Raineville IR, Rana HQ. Next-generation sequencing for inherited breast cancer risk: Counseling through the complexity. Curr Oncol Rep. 2014;16:371–82.
29. Hall MJ, Forman AD, Pilarski R, et al. Gene panel testing for inherited cancer risk. J Natl Compr Canc Netw. 2014;12(9):1339–46.
30. Yurgelun MB, Allen B, Kaldate RR, et al. Identification of a variety of mutations in cancer predisposition genes in patients with suspected Lynch Syndrome. Gastroenterology. 2015;149:604–13.
31. Desmond A, Kurian AW, Gabree M, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. JAMA Oncol. 2015;1(7):943–51.
32. Norquist BM. More genes, more problems? Benefits and risks of multiplex genetic testing. Gynecol Oncol. 2013;139:209–10.
33. Economopoulou P, Dimitriadis G, Psyrri A. Beyond BRCA: new hereditary breast cancer susceptibility genes. Cancer Treat Rev. 2015;41:1–8.
34. Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni syndrome. 1999 Jan 19 [Updated 2013 Apr 11]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1311/.

35. Apostolou P, Fostira F. Hereditary breast cancer: the era of new susceptibility genes. Biomed Res Int. 2013;2013:747318. doi:10.1155/2013/747318 Epub 2013 Mar 21.
36. Pilarski R. Cowden syndrome: a critical review of the clinical literature. J Genet Counsel. 2009;18:13–27.
37. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7.
38. Eng C. PTEN hamartoma tumor syndrome. 2001 Nov 29 [Updated 2016 Jun 2]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1488/.
39. McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers syndrome. 2001 Feb 23 [Updated 2016 Jul 14]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1266/.
40. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209–15.
41. Pharoah PD, Guilford P, Caldas C. International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121(6):1348–53.
42. Kaurah P, Huntsman DG. Hereditary diffuse gastric cancer. 2002 Nov 4 [Updated 2014 Jul 31]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1139/.
43. Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol. 2016;13:581–8.
44. Petrucelli N, Daly MB, Feldman GL. BRCA1 and BRCA2 hereditary breast and ovarian cancer. 1998 Sep 4 [Updated 2013 Sep 26]. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/.
45. King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302(5645):643–6.
46. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 1994 19;343(8899):692–5.
47. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105(11):812–22.
48. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329–33.
49. Rich TA, Woodson AH, Litton J, Arun B. Hereditary breast cancer syndromes and genetic testing. J Surg Oncol. 2015;111(1):66–80.
50. Easton DF, Pharoah PDP, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372(23):2243–57.

http://www.springer.com/978-3-319-59197-1

Managing BRCA Mutation Carriers

B. Chagpar, A. (Ed.)
2017, XI, 242 p. 24 illus., 21 illus. in color., Hardcover
ISBN: 978-3-319-59197-1