Management of the Patient with a Genetic Predisposition for Breast Cancer

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31.1 Hereditary Breast Cancer

Women who have close relatives with breast cancer have an increased risk of developing breast cancer themselves. Familial clustering of breast cancer may occur for several reasons. Breast cancer is a common disease, and clustering may be coincidental. Shared environmental or lifestyle factors may result in multiple cases of breast cancer within a family, particularly among siblings. Genetic risk factors are also known to explain some familial breast cancer clustering. While there has been a significant increase in genetics knowledge since *BRCA1* and *BRCA2* were identified over 25 years ago with additional genes now known to be associated with breast cancer risk, a large proportion of the family histories of breast cancer remain unexplained by current genetic testing. The ways we assess patients for hereditary breast cancer risk and the scope of genetic testing available have changed dramatically in the last few years. Understanding both the improvements and limitations of hereditary cancer assessment are crucial to provide appropriate risk management recommendations for patients. This chapter will review the basics of cancer genetics, outline selected genes associated with hereditary breast cancer, and discuss the importance of the family and personal history in identifying those who may have an inherited predisposition to breast cancer. Models for assessing the risk of developing cancer and of having a genetic predisposition to cancer will be described. Management of individuals at increased risk of breast cancer will be discussed, including genetic counseling and testing, interpretation of results, and options for modifying risk in those with a family history of breast cancer, with or without an identifiable gene mutation.

31.1.1 Somatic and Germline Genetics

All cancer is genetic; that is, all cancer is caused by the accumulation of genetic mutations in a specific cell line. Infrequently, cancer can be the result of a gene mutation that was inherited or occurred very shortly after conception (i.e. the mutation is present in every cell of the body). These types of mutations are called *germline* mutations. It is estimated that 5–10 % of all breast cancer cases are due to an inherited genetic factor that confers a high breast cancer risk [1]. Families with an inherited predisposition to cancer usually have more cases of cancer than would be expected by chance; cancer in several generations and cancer at earlier ages than are typical. Genetic testing for hereditary cancer predisposition most often requires a blood or buccal sample from the patient and looks for germline mutations. *Somatic* mutations typically occur during a person's lifetime and are thus not present in every cell in the person's body. Most tests that examine the genetics of a tumor are looking specifically for somatic mutations—mutations that are present in the cells that became cancerous but are typically not present in the rest of their cells (such as their germline (egg or sperm) cells). The purpose of these tests is not to identify hereditary cancer predispositions but to identify mutations within the tumor that could be potential therapeutic targets. However, if a patient has a germline mutation predisposing her to develop cancer, it should in theory be present in all of her cells, including their tumor cells. Some patients have first come to attention for hereditary cancer assessment due to an unexpected mutation identified in their tumor that was later determined to be germline [2]. On the other hand, due to differences in sequencing techniques and mutation reporting between tumor and germline genetic tests and the genetic alterations inherent in tumor formation, it is possible that a patient may have a germline mutation that is not

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detected/reported on tumor sequencing. If a patient is appropriate for hereditary cancer evaluation, she should be referred for genetic counseling and germline mutation testing, regardless of the tumor sequencing results. Also, if a mutation is detected in a patient's tumor and there is concern that the mutation may be germline, she should be referred for genetic counseling and germline mutation testing [2].

31.2 Genes Associated with Hereditary Breast Cancer

There are numerous genes that, when mutated in the germline, confer a significant risk for cancer, including several that increase the risk for breast cancer. Mutations in some genes confer high risks for breast cancer (defined here as causing over a fourfold increase in lifetime female breast cancer risk). More genes have been identified in the past 10 years whose mutations confer a more moderate increase in breast cancer risk (often defined as conferring at least a twofold increase in breast cancer risk). As of yet, there is no strict consensus on what constitutes a "high" versus "moderate" breast cancer risk, but similar cutoffs have been used in recent research and reviews [3]. We have divided these genes into these two risk categories to highlight differences in the assessment and management of mutations carriers. Table 31.1 identifies the genes whose mutations confer a high breast cancer risk while Table 31.2 provides an overview of genes associated with moderate risk. Other genetic changes, such as SNPs (single-nucleotide polymorphisms) have been associated with smaller alterations in breast cancer risk [4]. It is unclear how or whether an individual's breast cancer screening should be altered on the presence of an individual SNP. However, current research is exploring the incorporation of SNP data into comprehensive breast cancer risk assessment (including breast density and other risk factors) called a polygenic risk score [4, 5]. Clinical incorporation of polygenic risk scores may provide future refinement to currently available risk assessment techniques.

Most germline mutations that predispose to breast cancer are inherited in an autosomal dominant fashion, such that a mutation from either parent increases the risk for cancer. Spontaneous mutations are rare. Therefore, if an individual has a mutation, one of the parents is almost always a carrier, and siblings and children are each at 50 % risk of inheriting the familial mutation. Most of the genes are tumor suppressor genes which, when working properly, reduce the risk of developing cancer. When mutated, however, the protective function is lost and the risk of cancer is increased.

The risk for the development of cancer associated with mutations in these genes varies depending on the specific gene and the population analyzed. Early studies, which evaluated families based on a clinical ascertainment of four or more breast cancers, suggested a higher penetrance [6] than subsequent studies in families with a more modest family history [7]. Population-based studies test all individuals diagnosed with breast cancer for gene mutations, without regard to family history. In these studies, the risk for cancer in relatives is still lower [8]. It is likely that modifying genes or environmental factors affect penetrance from family to family.

Table 31.1 Hereditary breast cancer predispositions: high-risk

Gene (condition)	Approximate lifetime breast cancer risk for women	Other cancer risks and features
BRCA1 (Hereditary breast and ovarian cancer syndrome)	50–80 %	Cancers: ovary, prostate
BRCA2 (Hereditary breast and ovarian cancer syndrome)	50–80 %	Cancers: ovary, breast cancer in males, prostate, melanoma, pancreas
PTEN (Cowden syndrome)	25–50 %	Cancers: endometrial, thyroid (nonmedullary), colon, urinary tract Other features: macrocephaly, colon polyps (hamartomas, ganglioneuromas, juvenile polyps), skin lesions
CDH1 (Hereditary diffuse gastric cancer)	39–52 % (lobular breast cancer)	Cancers: gastric cancer (diffuse type); unclear if colon cancer risk is also increased
STK11 (Peutz-Jeghers syndrome)	45 %	Cancers: pancreas, colon, ovary, cervix, lung Other features: abnormal melanin deposits (lips, buccal mucosa, fingers, etc.)
TP53 (Li-Fraumeni syndrome)	High, but unclear due to rarity and high risks for many forms of cancer	Cancers: brain, adrenal cortex, sarcomas, leukemia, lung, GI tract; women have over a 90 % lifetime risk to develop cancer of some type
PALB2	35–60 %	Unclear if risk also increased for pancreatic cancer, ovarian, male breast cancer, or prostate cancer

Table 31.2 Moderate-risk genes

Gene	Approximate lifetime breast cancer risk for women (%)	Other cancer risks and features
ATM	30–40	Possible association with pancreatic cancer. Biallelic mutations cause ataxia-telangiectasia syndrome
CHEK2	20–45	Moderate colon cancer risk. Other moderate cancer risks possible (prostate, male breast cancer, etc.) Common founder mutation in Northern European ancestry = 1100delC
NBN	23	Unclear if other cancer risks present. Common founder mutation in Slavic population = c.657del5. Biallelic mutations cause Nijmegen breakage syndrome

Clinic-based ascertainment may select for families in which there is not only a gene mutation conferring breast cancer risk, but other genetic or environmental factors at play.

31.2.1 Hereditary Breast Cancer Predispositions: High-Risk

Table 31.1 summarizes the genes whose mutations confer high risks for breast cancer. Besides conferring a high risk for breast cancer, the majority of these gene mutations confer high risks for other forms of cancer. Most of these genes were associated with cancer risk over 20 years ago, so extensive research and clinical management recommendations are available [9].

The most common cause of hereditary breast cancer remains mutations in *BRCA1* or *BRCA2* which cause Hereditary Breast and Ovarian Cancer syndrome. A *BRCA1* or *BRCA2* mutation is found in approximately 1 in 300 to 1 in 800 Caucasians and about 1 in 40 individuals of Ashkenazi Jewish ancestry [8–10]. The rate in other ethnic groups is not well defined, although specific founder mutations have been identified in many countries, including the Netherlands [11] and Iceland [12]. *BRCA1* and *BRCA2* mutations are associated with a lifetime risk for female breast cancer of about 50–80 % in women [6, 13–15]. The lifetime risk for ovarian cancer in women is approximately 40–60 % with a *BRCA1* mutation and 20–30 % with a BRCA2 mutation [6, 13–15]. Men with *BRCA1* or *BRCA2* mutations also have an increased risk for breast cancer (up to 7 % lifetime risk with *BRCA2*; less with *BRCA1*) [16]. *BRCA1*-associated cancers are typically high grade, often with medullary features, usually estrogen and progesterone receptor negative, and do not overexpress HER2/neu (so-called "triple negative" breast cancer) [17]. *BRCA2*-associated breast cancers are generally estrogen receptor positive and of no specific histologic type [18, 19]. The ovarian cancers in *BRCA* mutation carriers are epithelial in origin and usually of serous histology [20, 21]. Fallopian tube cancers and primary peritoneal cancers are also prevalent; there is some evidence that the ovarian cancers associated with *BRCA1/2* mutations may originate in the fallopian tubes [22, 23].

Mutations in the *BRCA1* and *BRCA2* genes confer risks for cancers other than breast and ovarian. *BRCA2* mutations are associated with an increased risk of melanoma, pancreatic cancer, and prostate cancer [6, 24, 25]. Prostate cancer occurring in both *BRCA1* and *BRCA2* mutation carriers may be more aggressive than prostate cancers in the general population [26–28]. While very rare, biallelic mutations in *BRCA2* (i.e., a mutation on both the maternal and paternal alleles of the gene) are known to cause Fanconi Anemia; this occurs with biallelic mutations of many of the genes in the same pathway as *BRCA2* [29].

Cowden syndrome is caused by a mutation in the *PTEN* gene. It is often first recognized because of skin lesions and intestinal hamartomas [30], but is also associated with an increased risk of early-onset breast cancer that ranges from 25 to 50 %; newer studies indicate the lifetime risk may be higher than 50 % [31]. Besides breast cancer, nonmedullary thyroid cancer, endometrial cancer, colon, renal cancer, and possibly melanoma are increased [31, 32]. Benign findings that occur frequently include benign thyroid disease, trichilemmomas, which are flesh-colored bumps on the face and tongue, and macrocephaly above the 97th percentile [33].

Li-Fraumeni syndrome is a rare disorder caused by a mutation in *TP53*, the "guardian of the genome," that prevents cells with DNA damage from proceeding through the cell cycle. Somatic mutations in *TP53* are found in about half of all cancers. When present as a germline mutation, risk for cancer is extremely high [34, 35]. Approximately 50 % of individuals with mutations have developed cancer by age 30, and the prevalence by age 70 is 90 % [36]. Osteosarcomas, soft tissue sarcomas, brain tumors, leukemia and adrenal cortical carcinomas are the characteristic tumors, with breast cancer found in 25 % of those who do not die of childhood tumors [37]. Breast cancer tends to occur very early, often in the 20s. Virtually every other solid tumor is also found at very early ages in this population, with multiple primary tumors found in 57 % in a 30-year follow-up study [38]. New screening protocols have been created to address the multi-system cancer risks associated with Li-Fraumeni syndrome, incorporating brain and whole body MRI, in addition to mammogram and breast MRI, colonoscopy, and dermatology exams [39].

Peutz–Jeghers syndrome is caused by mutations in *STK11*. It is usually diagnosed based on distinctive hamartomatous polyps [40] and the presence of benign pigmented spots on the lips and buccal mucosa. The lifetime risk for cancer is up to 80 % in these families, with breast cancer being the most common at around 45 % [41–43].

Historically, mutations in *CDH1* have been associated with Hereditary Diffuse Gastric Cancer and confer a very high lifetime risk (67–83 %) for gastric cancer [9, 44]. Due to limitations in endoscopic surveillance, prophylactic gastrectomy is recommended for CDH1 mutation carriers in their early 20s [45]. Women with *CDH1* mutations also have between a 39 and 52 % lifetime risk for lobular breast cancer [9, 44]. With the advent of multigene testing for hereditary breast cancer risk, increasing numbers of individuals have been identified with *CDH1* mutations with no known family history of gastric cancer. This creates a dilemma for appropriate gastric cancer risk assessment and management as these families may not have the same high gastric cancer risks [46].

PALB2 was first identified in 2006 [47]. Recent studies have indicated that women with a *PALB2* mutation have a similar breast cancer risk to women with a *BRCA2* mutation [48]. The strength of an individual's family history of breast cancer appears to have a bearing on the degree of cancer risk conferred by a *PALB2* mutation [48]. *PALB2* mutations also appear to be associated with moderately increased risk for pancreatic cancer, although further research is needed to delineate this [49]. Currently, it is unclear if mutations in *PALB2* increase the risks for other cancers, such as male breast and ovarian [48]. Like with *BRCA2* mutations, biallelic *PALB2* mutations are known to cause Fanconi Anemia [50].

31.2.2 Hereditary Breast Cancer Predispositions: Moderate-Risk

Table 31.2 summarizes information on three genes whose mutations confer moderately increased breast cancer risks. For *ATM*, *CHEK2*, and *NBN* mutation carriers, NCCN (National Comprehensive Cancer Network) has made management recommendations [9]. Breast cancer risk management guidelines have also recently been released for individuals with mutations in *NF1* (which causes Neurofibromatosis Type 1); these are not reviewed here as many individuals with *NF1* mutations are identified through pediatric genetics evaluation [9]. Many more genes are suspected of conferring similar (or slightly lower) breast cancer risks; however, consensus management guidelines do not yet exist for mutation carriers [3]. Testing of these genes is often included on commercially available multigene tests, which can create difficulties for clinicians and patients in interpreting the results and determining clinical utility.

Biallelic mutations in *ATM* have been known for many years to cause the neurodegenerative disorder, Ataxia-telangiectasia [51]. Increasing numbers of studies have found that women with a monoallelic mutation of ATM have a two-threefold increase in breast cancer risk [52]. However, individuals with a missense mutation in certain key functional domains of *ATM* may have significantly higher breast cancer risks [53]. Carriers of one *ATM* mutation may also have a moderately increased risk for pancreatic cancer, but this and any other potential cancer risks require further definition [54].

The majority of data available on *CHEK2* mutation cancer risks stems from a common founder mutation (1100delC) present in 0.5–1.3 % of individuals of Northern European descent [55, 56]. The female breast cancer risk conferred by this mutation is estimated to be approximately threefold, but like mutations in *PALB2*, *ATM*, and *NBN* the exact magnitude can vary depending on a person's family history of breast cancer [55]. *CHEK2* mutations appear to predispose primarily to estrogen receptor positive breast cancers [55]. Other pathogenic mutations in *CHEK2* beyond 1100delC are expected to confer similar breast cancer risks. The risks for other cancers are still being delineated, although moderately increased risks for multiple other cancers (including colon and prostate) have been indicated in some studies [57].

Like *CHEK2*, *NBN* also has a common founder mutation, c.657del5, in the Slavic population [58]. This monoallelic mutation appears to confer a 2.7 fold increase in female breast cancer risk [3, 58]. As is the case with both *ATM* and *CHEK2*, some missense mutations in NBN appear to confer similar or greater breast cancer risks than truncating mutations [58]. Individuals with biallelic NBN mutations have a condition called Nijmegen breakage syndrome, which is characterized by microcephaly, cognitive impairment, immunodeficiency and increased cancer risks [59].

31.3 Identification of Individuals at Increased Risk for Breast Cancer

31.3.1 Family History

A woman's risk of developing breast cancer is strongly related to the number of affected relatives, their genetic proximity, and ages at which they were diagnosed. Collecting an accurate family history is the single most cost-effective approach to identifying individuals with hereditary breast cancer [60]. A three-generation family history should be collected on individuals who have a suspected predisposition to cancer and should include all first-degree relatives (children, siblings, parents) and second-degree relatives (uncles and aunts, nieces and nephews, grandparents), as well as more distant relatives who have cancer [61]. For each family member, essential information includes current age or age and

cause of death, medical history including types of cancer and age of onset, ethnicity/country of origin, and other syndrome-specific features, for example multiple gastrointestinal polyps. A graphic representation of the family history using recognized pedigree nomenclature outlined in Fig. 31.1 allows assessment of inheritance patterns and permits this information to be communicated to other clinicians and to patients in a clear and consistent manner [62].

The cancer pedigree should include at least the number and gender of individuals in each generation, whether affected with cancer or not, so the ratio of affected to unaffected family members can be incorporated into the assessment. A common breast cancer genetic myth is that "you don't have to worry about breast cancer on your father's side of the family." It is essential to collect *both* maternal and paternal histories of cancer, since germline mutations are equally likely to be inherited paternally as maternally.

Knowledge of breast cancer in first-degree relatives is generally accurate [63], but is less reliable in more distant relatives [64, 65]. Knowledge of cancers in other organs is often less precise. Gastric cancer and ovarian cancer may both be reported as "stomach cancer," and cervical, uterine, and ovarian all reported as "female cancer." Ovarian cysts may also be misreported as cancer. Questioning the patient about outcomes may be helpful in determining the accuracy of the diagnosis. For example, a report of a relative with long-term survival after a diagnosis of "ovarian cancer" or "pancreatic cancer" should raise questions about the accuracy of the diagnosis since these cancers have low long-term survival rates. Family medical histories are dynamic, and it is important to remind the patient that if additional cases of cancer are diagnosed or discovered, they should recontact the provider because the new information may alter the risk calculation and subsequently alter recommendations for risk management [66].

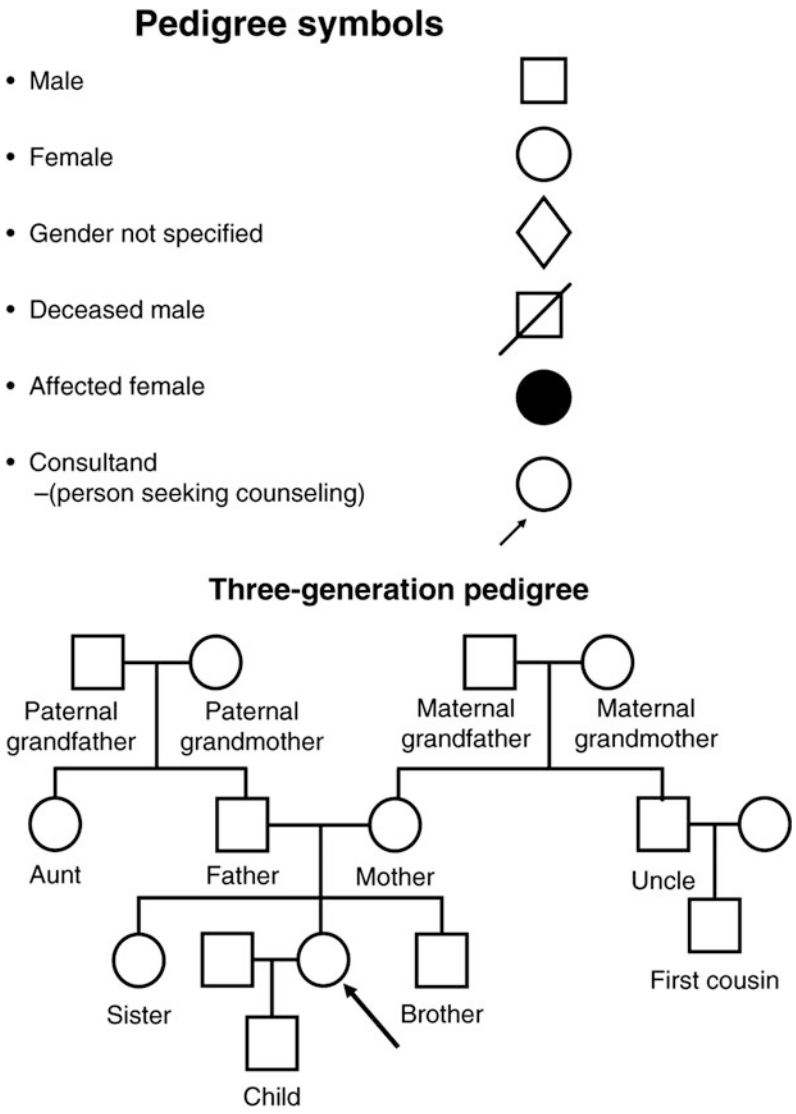

Fig. 31.1 Pedigree symbols and structure (represented by two slides). By using recognized pedigree nomenclature and structure, family history information can be communicated to other clinicians and patients in a clear and concise manner

Taking a detailed family history takes time. Some centers use a questionnaire that can be mailed prior to an appointment or completed in a waiting room. Several web-based questionnaires in both English and Spanish are readily available from resources such as the Centers for Disease Control and Prevention (http://www.hhs.gov/familyhistory/). Some centers utilize software such as Hughes Risk Apps (http://www.hughesriskapps.com/riskclinic.php) or Progeny (http://www.progenygenetics.com/) to create digital pedigrees. In some cases, small family size, adoption, and misidentified paternity complicate the analysis of a family history [67]. Despite these difficulties, obtaining an accurate family history reduces the likelihood of either overlooking the possibility of a hereditary cancer syndrome, which in turn leads to lost opportunities for cancer risk management and risk reduction in the patient as well as extended family members; or of inappropriately performing genetic testing. After obtaining an initial family history, referral to a cancer genetic service may be the most appropriate way to obtain a complete family history and risk assessment.

31.3.2 Personal Health History

In addition to information about the extended family, a cancer risk assessment includes a personal health history. The presence of cancer, cancer site, age of onset, the existence of multiple primaries or bilaterality, history of previous biopsies and whether the biopsy showed proliferative breast disease are important. Hormone-related factors such as age at menarche, nulliparity or age at first birth, number of pregnancies, duration of breast-feeding, age of menopause, and exogenous hormone use (oral contraception, hormone replacement therapy) also have an impact on the risk of developing cancer. Diet and exercise play a significant role in the development of breast cancer, not least of which is the impact of obesity on the increased rate of breast cancer in postmenopausal women [68]. Alcohol ingestion is also positively associated with breast cancer [69, 70]. Mammographic breast density is a recognized risk factor for breast cancer, and may be more strongly correlated with a risk for the development of breast cancer than any factors except for age, gender, and the presence of a breast cancer predisposition gene mutation [71]. Finally, radiation exposure, particularly during childhood and adolescence, increases the risk of breast, thyroid and other cancers [72]. Radiation was commonly administered in the 1940s through early 1970s for acne vulgaris, tinea capitis, hemangiomas, and enlargement of the tonsils or thymus, as well for Hodgkin's disease and other malignancies [72, 73]. The identification of a woman with both breast and thyroid cancer may suggest Cowden's syndrome, but in the presence of a history of radiation therapy, an environmental cause would be far more likely than an inherited one.

31.4 Risk Assessment

Two different but related risks are important to the individual patient: the risk of developing breast cancer, and the risk of carrying a mutation in a breast cancer predisposition gene.

Communication of risk requires an understanding of ways to present risk, the various models used to assess risk, the manner in which numbers can be interpreted, and the factors that are necessary to put them into context of the patient's perception of risk. Most women with a family history of breast cancer significantly overestimate their risk [74].

31.4.1 Absolute Risk

An absolute risk is the probability of an event occurring during a specific interval. For example, a well-known risk figure associated with breast cancer is 12 %, a cumulative incidence statistic, which means that about one in eight women in the general population will develop breast cancer at some point in her lifetime. Unless she has a breast cancer predisposition gene mutation, a woman who is presenting for risk assessment at age 30 has an absolute risk of developing breast cancer in the next 5 years of about 0.1 %, or one in a thousand, far less than the 12 % lifetime statistic [75].

31.4.2 Relative Risk

Most population-based studies of familial cancer report absolute risk, which compares the frequency of cancers within affected families to the frequencies expected in the general population. An observed-to-expected ratio (odds ratio) is used to quantify the risk [76] based on the particular environmental factor (parity, oral contraceptive use, diet, pesticide exposure) or the genetic proximity of an affected relative (sister, mother, aunt, grandmother). The risk is typically described as x-fold over that of the general population, such as a twofold risk for women with a sister diagnosed with postmenopausal breast cancer [77]. The degree of risk is influenced by the closeness of the relative and the age of diagnosis of breast cancer [77]. This may also be reported as a percent increase. Hormone replacement therapy may confer a relative risk of 1.2, for example, which is accurately reported as a 20 % increase in the risk. That concept is not always well-understood by patients who are confused and call their doctors wondering if their risk has increased from 12 to 32 % by their use of postmenopausal hormone replacement therapy, when a 1.2 relative risk has only increased their risk from 12 to 14 %.

31.4.3 Predicting Development of Breast Cancer: Gail Model and Claus Tables

Several mathematical models have been developed to estimate the risk of developing breast cancer. The Gail model computes individualized absolute risk in women receiving routine mammograms [78]. It uses six specific risk factors (age at evaluation, age at menarche, age at first live birth, number of prior breast biopsies, presence of proliferative breast disease on biopsy, and number of first degree relatives with breast cancer) to estimate 5-year and lifetime risk [79]. Although the model is a useful tool for defining risk estimates in the general population, it has several limitations in the context of a high-risk setting. It does not address the risk for women under age 35 or for those who are not undergoing regular mammograms. Most relevant to a high-risk population, the Gail model includes only first-degree relatives and therefore does not include paternal history, nor does it include a family history of ovarian cancer or age of onset of cancers. Therefore, it is not an appropriate model to assess risk for women in families with a known or suspected inherited cancer predisposition gene mutation.

The Claus tables [80] were subsequently developed based solely on family relationships and are more appropriate for estimating risk in women with a family history of breast cancer. This model includes first-and second-degree relatives and can be used to estimate cumulative risk over 10-year intervals. It includes relatives in only one lineage (either maternal or paternal) but not both. The model uses a single locus dominant genetic assumption, but those cases are limited to only about 5–10 % of breast cancers.

31.4.4 Models for Predicting Presence of a Gene Mutation and Cancer Development: BRCAPro, BOADICEA, and Tyrer-Cuzick

The most significant risk for breast cancer, except for gender and age, is the presence or absence of a specific germline mutation. Therefore, an important step in the risk assessment is to determine the likelihood that the family has a recognizable genetic mutation, as outlined in Tables 31.1 and 31.2 and discussed above. *BRCA1/2* gene mutations are the most prevalent of the genetic breast cancer predispositions. Due to this, most models currently available assess for BRCA1/2 mutation risk only and do not calculate a person's chance of having a mutation in another breast cancer predisposition gene.

The most commonly used model in the U.S. is BRCAPro, which includes age-specific cancer as well as positive and negative family history information of both first-and second-degree relatives from both sides of the family [81–83]. The information is then evaluated using a Bayesian approach to calculate carrier probabilities. Free registration for online access to this model is available at https://www4.utsouthwestern.edu/breasthealth/cagene/ as part of the CancerGene software package.

Another model, used widely in the U.K. and Australia, is BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), which was developed based on segregation analysis of breast and ovarian cancer [84]. Recent updates have added risk assessment for mutations in *CHEK2, ATM,* and *PALB2*—currently BOADICEA is the only model that provides specific risk estimates for mutations in these genes [85]. A user-friendly web-based program (http://www.srl.cam.ac.uk/genepi/boadicea_home.html) is available.

31.5 Genetic Testing

Genetic testing for a hereditary breast cancer risk has become increasingly complicated with the introduction of multigene tests [3]. Next-generation sequencing technology has greatly reduced the cost of genetic testing and allows for numerous genes to be analyzed in a single test. However, testing a mixture of genes associated with high or moderate breast cancer risks complicates the interpretation of results. Not all genes currently analyzed on commercially available tests have consensus guidelines for management of mutation carriers. Increasing the number of genes tested also increases the chance that a variant of uncertain significance will be detected. While comprehensive genetic testing is now easier to obtain than ever before for patients, thought and caution must still be exercised in identifying the best testing candidate in the family and in the results interpretation. Depending on the circumstances of testing, a negative (normal) test does not always lower the risk for breast cancer and should not always be considered "good news." Many families deemed to be appropriate for genetic testing have a sufficiently strong family history that warrants enhanced screening, even if no mutation is found [9]. Patients seek genetic testing for many reasons and the impact of the test result—whether positive, negative, or uninformative—on psychological health, social relationships and medical care needs to be explored prior to testing [86]. In addition, the test result has implications not only for the individual being tested, but for family members. As such, there is an ethical requirement to inform family members, and a strategy for doing so must be developed. Due to the complexities of genetic testing and the significant implications of the test results on patients and their family members, referral to a genetic professional can be very beneficial and is recommended by multiple organizations (NCCN, ACS, etc.). A list of genetic counselors can be found

at http://www.nsgc.org or a cancer center can be located at the National Cancer Institute's website (http://www.cancer.gov/search/geneticsservices/). While more clinics and hospitals employ genetic counselors than ever before, genetic counseling services are also being made available by telemedicine or telephone to increase accessibility [87].

In general, referral for genetic testing is appropriate for an individual diagnosed with breast cancer at/under age 45, bilateral breast cancer, male breast cancer, or both breast and ovarian cancer. Families with two or more individuals with breast cancer under age 50, breast cancer under age 50 and ovarian cancer at any age, or three or more individuals with breast or pancreatic cancer at any age are also appropriate for genetic counseling and testing [9]. Some families have fewer cases of cancer but have a small number of women, or have related cancers such as pancreatic cancer, advanced prostate cancer, or melanoma. These may also be appropriated for genetic testing [67]. New data suggests that individuals of known Ashkenazi Jewish ancestry may consider testing for the three common *BRCA1/2* founder mutations regardless of reported personal or family history of cancer [88]. Ideally, the first person to receive genetic testing in a family should be someone affected with cancer, because if there is a mutation in the family, that person is more likely to carry the mutation than unaffected individuals. If a mutation is identified, testing for that specific gene mutation can then be performed in relatives, both male and female, based on the inheritance pattern of the particular gene. Testing for a known familial mutation is currently cheaper than full sequencing/deletion duplication testing of a gene, so if a mutation has already been identified in a family, it is typically most appropriate and cost-effective to only test relatives for the known mutation.

If a mutation is identified in a family, it is ideal from a scientific and psychosocial perspective to test other branches of the family, starting with the oldest generation alive. For example, rather than testing all cousins of a mutation carrier, testing aunts and uncles provides information for their descendants. If a parent has a mutation, all children, regardless of their cancer status, become testing candidates; if there is no mutation, subsequent generations do not need to be tested. From a psychosocial perspective, there are also advantages to testing a member of the oldest generation first, because it is often easier to share information from a parent to a child than from a child to a parent [89].

Since the 2013 Supreme Court decision regarding gene patenting, multiple laboratories in the U.S. offer genetic testing for hereditary breast cancer predispositions [3]. Testing can include *BRCA1/2* only or multiple genes associated with high and moderate breast cancer risks on a single test. The number of genes tested, as well as testing methodologies, variant classification methods, cost/billing, and financial assistance programs for patients vary between laboratories. A resource to help identify available laboratories for other cancer-related germline tests is GeneTests (www.genetests.org), available free of charge. This website, developed by the University of Washington, Seattle with funding from the National Library of Medicine and Maternal and Child Health Bureau, is an information resource that includes a directory of clinical and research laboratories that offer specific medical genetic tests.

31.5.1 Genetic Counseling

Prior to having a specimen obtained for genetic testing, genetic counseling is recommended and is now required in some cases to obtain insurance coverage for testing [9]. The purpose of genetic counseling is twofold: to provide genetic education and address psychosocial concerns. During a genetic counseling appointment, an individual will receive information on cancer etiology and a detailed risk assessment based on their personal and family history. The person's risk to develop cancer (or another cancer) and the chance to have an identifiable mutation in a cancer predisposition gene will be explored. A discussion will be had regarding the implications of genetic testing for both the individual and their family.

Genetic counseling involves interactive discussion about what the individual is hoping to learn from their risk assessment and what actions they are interested in pursuing (genetic testing, screening, cancer risk reduction). Many individuals have high expectations of what genetic testing can tell them about their cancer risks, when the reality may be quite different [90]. A frank discussion of the benefits and limitations of genetic testing is crucial to facilitating fully informed consent prior to pursuing genetic testing. A tailored plan is created with the patient for their cancer screening and risk reduction, regardless of whether or not they elect to pursue genetic testing. If the individual elects to pursue genetic testing, the genetic counselor can help coordinate this and create a plan for discussion of results.

Individuals differ in their belief on whether the identification of a mutation is good or bad news. For a woman with breast cancer, having a mutation may be good news in that it explains the etiology of her cancer. On the other hand, an unaffected woman who is the only one of her four sisters without a mutation may experience survivor guilt and see her result as bad news. Exploring the potential reactions to test results is an important part of the pretest session.

The genetic counseling process provides individuals the chance to express their interests and concerns about genetic testing. Some individuals are hesitant to consider genetic counseling and testing because of concerns regarding genetic discrimination [91]. Both federal and state laws have been passed that protect genetic privacy. In May 2008, the

Genetic Information Nondiscrimination Act was signed into law, and went into effect in May 2009 related to health insurance and in November 2009 related to workplace issues [92]. Through these laws, most individuals in the U.S. are protected from genetic discrimination as it relates to health insurance and employment. Currently, most individuals are not protected from potential genetic discrimination regarding life or disability insurance. However, while life insurance policies may inquire about genetic disorders within a family, they are more likely to inquire generally about family history (i.e., if a family history of cancer exists, etc.). Individuals with a personal or family history of cancer are already at risk to experience life or disability insurance discrimination based on family history whether or not they undergo genetic testing, which may put the potential risks of discrimination on the basis of genetic test results into perspective. Although the consequences of genetic discrimination may be significant, there are few documented cases of such discrimination, and the risk is likely to continue to diminish as genetic testing for adult conditions becomes more common. Other individuals elect not to pursue genetic testing due to financial cost. This barrier is diminishing with decreasing testing costs and financial assistance provided by many laboratories. Whether or not a person would alter their medical management on the basis of genetic test results and whether the person has any living relatives who would benefit from the information also plays a role in genetic testing decisions.

Most hereditary breast cancer predispositions (with the exception of Li-Fraumeni syndrome and some features of Cowden syndrome) are adult-onset. In the absence of documented medical benefit, offering genetic testing to minors for an adult-onset condition may compromise the autonomy of the child. Psychological consequences could include stigmatization of the child, or viewing the child as fragile [93, 94]. Due to these concerns, genetic testing for adult onset conditions is not recommended for minors. Most parents do discuss their genetic test results with their children in an age appropriate manner [95]. This can help children understand the screening/risk reduction measures their parent may be undertaking and help prepare them for their own future health decisions. Genetic counselors can assist individuals with strategies for disclosing their genetic test results to children and extended family members. They can also connect families with support, research, and educational resources on a local or national scale.

31.5.2 Interpretation of Test Results

Three basic categories of results are possible from genetic testing: positive, negative, or variant of uncertain significance. Oftentimes, the word "mutation" was used to connote a pathogenic (i.e., damaging) genetic change, where the word "variant" designated a genetic change of indeterminate consequence. While we have used this terminology throughout the chapter due to its persistence in common usage, genetics nomenclature has shifted to using the term "variant" for any genetic change to provide consistency [96]. In this section, we will use the term "variant" as recommended to highlight how genetic test results are currently reported in clinical practice. A positive test result indicates that an individual has a variant that increases the risk of developing breast cancer, as well as other cancers or benign conditions associated with that mutation. This result also means that other family members are candidates for genetic testing. On a test report, a positive result will usually be listed as a "pathogenic" or "deleterious" variant (or mutation). Variants that are considered "likely pathogenic/deleterious" should be considered a positive test result for clinical management purposes [97].

A negative test result means that no variants were detected that were either uncertain or pathogenic. The significance of a negative test result depends on whether or not there is a known pathogenic variant in the family. If the pathogenic variant in the family is already identified, this result is a true-negative test result and means (with greater than 99 % accuracy) that the patient did not inherit that variant. In a family carrying a pathogenic variant that confers high cancer risks, a true-negative test result typically means the individual would have a risk of developing cancer similar to the risk of a person in the general population. This may not hold true if the pathogenic variant in the family confers moderate cancer risks. In many families, a pathogenic variant conferring moderate cancer risks does not track with all of the relevant cancer diagnoses in the family. Thus some of the familial cancer risk may not be explained by the moderate risk pathogenic variant. Management recommendations for true negative individuals from families with a pathogenic mutation conferring moderate cancer risks are still being determined and should take into consideration personal and family history factors. In both types of families, management recommendations should incorporate other risk factors for breast cancer, including those assessed by the Gail model as well as breast density and family history of breast cancer on the other side of the family.

The predictive value of a negative test in an individual diagnosed with the cancer of interest is lower if the patient is the first one in the family being offered testing. There are a number of possible explanations for a negative test result in this case, including the possibility that the cancers in the family are not due to an inherited gene mutation but rather chance occurrences; that limitations of the technology do not allow a variant to be identified; that the variant is in a gene different from the one analyzed; or that the susceptibility gene that is predisposing to cancer in that family has not yet been discovered. Another possibility is that there is a familial

gene variant accounting for the apparent increase in breast cancer; but that the individual tested does not have the mutation. In the presence of a striking family history, it may be appropriate to offer testing to a second affected family member. A result of "likely benign" or "likely polymorphism" is also clinically considered negative results [97].

A negative test result in an unaffected individual from a family that has not been previously tested provides limited information to the individual. Recommendations for risk management for this woman should be based on the family history [98].

Identification of a "variant of uncertain significance" means a genetic change has been found that may or may not increase the risk of cancer [97]. These results are common on multigene tests [3]. As more research is completed, most of these will be reclassified as either benign or pathogenic variants. Until the variant is reclassified, families with variants of uncertain significance should be managed based on family history. Unless testing is done for research purposes in an attempt to clarify the significance of the variant, testing other family members for the variant is typically discouraged since no clinically relevant interpretation can be derived from the result at this time. While standards for variant classification exist, laboratories may utilize different cutoffs from one another when determining when a variant would be considered benign, uncertain, or pathogenic [97]. This creates situations where one laboratory may call a variant uncertain while another laboratory calls the same variant pathogenic. Understandably, these varying interpretations create significant distress for clinicians and families. There is an increasing push for genetic laboratories to share data with the research community in anonymized public databases to facilitate resolution of these discrepancies. One such database, created by the NCBI, is ClinVar (http://www.clinvar.com/). Through this database, information on specific variants and their classification by submitting genetic laboratories can be reviewed. For clinicians, assessing the robustness of a genetic testing laboratory's variant classification system and commitment to research has become an increasing decision-point when choosing a laboratory for clinical use.

31.6 Medical Management of Breast Cancer Risk

Recommendations for medical management of individuals at increased risk for developing breast cancer, either because of family history or because of the presence of a known gene mutation, are based often on consensus and clinical judgment rather than randomized clinical studies [9]. Although the details vary, risk reduction options generally include enhanced screening, chemoprevention and surgical risk reduction.

31.6.1 Screening for Breast Cancer in Men

Men with a breast cancer predisposition gene mutation should be instructed remain aware of any changes in breast tissue and undergo clinical breast exam annually or semi-annually. Baseline mammogram may be considered in the presence of gynecomastia [9]. Although men with a BRCA mutation have a much higher risk of breast cancer than the general male population, it is less than half the risk for women in the general population, so routine imaging with mammograms or MRI is not currently part of the screening protocol in most centers.

31.6.2 Medical Management of a Woman with no Identifiable Mutation

Women without an identifiable mutation, who have a family history that includes only breast cancer, will have a risk of developing breast cancer based on empiric personal and family history data, such as that obtained from the a risk prediction model, or available literature [77]. In these families, first- and second-degree relatives of women with breast cancer should initiate annual mammograms 5–10 years before the earliest diagnosis in the family or age 40, whichever is youngest, but not before age 30. For women with a lifetime risk of breast cancer over 20 % (with most of the risk from family history), following a discussion about the increased risk of false positives, breast MRI should be offered annually for screening until their lifetime risk is beneath 20 % [9] In addition, since mammographic breast density (heterogeneously dense or extremely dense) makes interpretation of mammograms more difficult and also increases the risk of developing breast cancer [71], breast MRI may be an appropriate complement to mammogram in women with dense breasts and a family history of breast cancer, even if the risk does not reach 20 % by available mathematical models [98, 99]. In addition, chemoprevention or risk-reducing mastectomy, as discussed below, may be appropriate for some of these women [100]. Since the risk of ovarian cancer is not appreciably increased in breast-only histories, ovarian screening is not recommended.

31.6.3 Medical Management of High Risk Gene Mutation Carriers

The options for management include surveillance, chemoprevention and risk-reducing surgery. Most data come from carriers of mutations in *BRCA1* and *BRCA2,* but are generally appropriately applied to those with Cowden, Peutz-Jeghers, and Li-Fraumeni syndromes, and *PALB2* mutations except as noted. Each high risk mutation signifies other cancer risks in addition to breast cancer and screening for each individual cancer must be considered separately. Those other cancer risks are briefly described in Table 31.1 The efficacy of various options in reducing mortality is still being defined, and enrollment of high-risk subjects into research resources and clinical trials should be encouraged.

31.6.4 Medical Management of Moderate Risk Gene Mutation Carriers

Many new breast cancer predisposing mutations (Table 31.2) in genes such as *CHEK2* and *ATM* have been identified, and most of these increase the risk of breast cancer by 2-4-fold [3]. The long-term risks from these mutations are still being clearly refined, but many of these mutations increase a woman's risk of breast cancer above 20 % for her lifetime, and annual breast MRI in addition to annual mammogram is recommended. Women with these moderate risk mutations are not known to be at increased risk for ovarian cancer at this time, so risk reducing bilateral salpingo-oophorectomy (RRBSO) is not warranted. Additionally, the lifetime risks associated with moderate risk mutations are often not high enough to warrant risk reducing mastectomy, since most of these women will never develop breast cancer [9]. However some families with moderate risk mutations may have a more significant history of breast cancer than expected; in these families, risk-reducing mastectomy may be considered on a case-by-case basis [9]. Thus, consultation with a genetic counselor for these emerging mutations is strongly recommended and cautious decision making is required about risk reducing surgeries.

31.6.5 Screening for Breast Cancer in Women

In the general population, mammographic screening for breast cancer in women over age 50 has been proven to be effective in reducing breast cancer mortality. Screening between the ages 40 and 49 is controversial but generally recommended [101, 102]. Women with identifiable moderate and high risk mutations should undergo annual breast MRI and annual mammogram [9]. A randomized trial of MRI compared to mammogram among high risk women demonstrated the superiority of MRI with a sensitivity of 86 % compared to 18 % for mammogram, and that MRI diagnosed breast cancer at an earlier stage of breast cancer than with mammogram alone [103]. These factors act as a surrogate for the likely survival benefit of breast MRI given enough follow-up time. Breast MRI has lower specificity, resulting in a higher proportion of false positives, which is why women should be at a significant lifetime risk of breast cancer to warrant its use.

The age at screening initiation varies based on the yearly risks associated with each specific mutation (Table 31.3). Since breast cancer may occur earlier in women with Li-Fraumeni syndrome, screening begins at age 20–25 [9, 38]. For women with *BRCA1* or *BRCA2* mutation, annual breast MRI should begin at age 25. An observational study noted that women with BRCA mutations receiving mammograms before age 30 were at higher risk for breast cancer, presumably from radiation exposure, thus breast MRI is utilized exclusively among high risk women younger than 30 [104]. For women with a *PALB2* mutation, initiating screening at approximately age 30 is reasonable, based on available literature [9, 48]. Although *CDH1* and *PTEN* are high risk mutations, breast cancer risk increases at an older age, thus screening initiation is recommended at age 30–35 in carriers [9, 45]. The exact recommended age to initiate breast cancer screening for women with moderate risk mutations such as *ATM*, *CHEK2*, and *NBN* is still being determined, but starting around age 40 would be reasonable as this is when the breast cancer risk appears to start rising in carriers [9, 52, 55]. And for all mutation carriers, breast cancer screening should begin 5–10 years earlier than the earliest breast cancer that occurred in a close relative, if this would make screening start at an earlier age than the age ranges given above [9]. Breast MRI should be performed in a center that has a dedicated breast coil, experience in interpreting breast MRI and the ability to perform MRI-directed breast biopsies. Most centers alternate mammograms and MRI evaluations so that women receive some type of imaging every 6 months [105].

Although there is no proof that patient self-breast awareness or clinical breast examination reduces mortality from breast cancer in women either with or without a genetic predisposition to breast cancer, they are recommended components of screening for breast cancer [106]. The current recommendation is that women remain aware of any changes in their breasts and that clinical breast exam be performed bi-annually starting at age 25 (or earlier with Li-Fraumeni syndrome) for women at increased breast cancer risk [9]. The usefulness of clinical breast examination is related to the amount of time spent on the exam, and is most beneficial among women who do not have access to breast imaging [107]. In general, examination of both breasts should take approximately 3 min [108].

Table 31.3 Risk management according to breast cancer predisposing mutation

	BRCA1 BRCA2	TP53	PALB2	PTEN CDH1	ATM CHEK2 NBN
Age to start breast MRI	25	20–25	30	30–35	40
Age to start mammogram	30	30	30	30–35	40
Consider chemoprevention	Yes	Yes	Yes	Yes	Yes
Consider RRM	Yes	Yes	Yes	Yes	In some families
Consider RRSO	Yes	No	No	No	No

31.6.6 Chemoprevention for Breast Cancer

Tamoxifen is a selective estrogen receptor modulator that has been used since 1977 for treatment of breast cancer, both as adjuvant therapy and treatment of advanced disease. Women treated with tamoxifen were found to have a reduction in the incidence of contralateral breast cancer. This observation led to studies of tamoxifen as a breast cancer chemoprevention agent in women who were at high risk but did not have breast cancer. The largest such study, conducted by the National Surgical Adjuvant Breast and Bowel Project, demonstrated approximately a 50 % risk reduction in incidence of both invasive and in situ breast cancer in women who had an *a priori* 5-year risk of 1.7 % or greater as calculated by the Gail model [100, 109]. In observational studies, tamoxifen reduced breast cancer risk by 62 % among women with BRCA2 mutations; however, there is debate whether it is as effective among women with BRCA1 mutations [110, 111]. Only estrogen receptor-positive cancers are reduced with tamoxifen. There was no difference in the number of estrogen receptor-negative cancers [109]. Tamoxifen is associated with a doubling of the risk of endometrial cancer (from one to two cases per 1000 women per year) and a tripling of risk of pulmonary embolism (from 0.23 to 0.69 per 1000 women per year), both primarily in postmenopausal women. A second study, The Study of Tamoxifen and Raloxifene (STAR) demonstrated that raloxifene, another selective estrogen receptor modulator, provided benefits similar to tamoxifen in reducing the risk of invasive breast cancer, although in situ cancer was not reduced [112]. Exemestane and anastrazole, aromatase inhibitors have been shown to reduce the risk of breast cancer similarly to tamoxifen, however there are not long-term data yet. Aromatase inhibitors have never been compared directly with SERM's, and they increase the risk of osteoporosis, making the use of aromatase inhibitors as prevention agents more problematic [113, 114].

The use of chemoprevention agents in women with gene mutations is not well studied [111], however prospective observational data show that women with BRCA1/2 mutations who were treated adjuvantly with tamoxifen for breast cancer yielded about a 50 % reduction in the risk of a second breast cancer in the contralateral unaffected breast. In women with a family history of breast cancer but without an identifiable breast cancer predisposition gene mutation, either tamoxifen or raloxifene is recommended if the risk by the Gail model is over 1.7 %. Women with a family history of breast cancer, but no affected first-degree relatives, or women with dense breast tissue, may have a calculated risk lower than 1.7 %, but chemoprevention may still be appropriate.

31.6.7 Risk-Reducing Salpingo-Oophorectomy

Risk of ovarian cancer is greatly increased in families with *BRCA1* and *BRCA2* mutations, at about 40 % in *BRCA1* mutation carriers and 10–30 % in *BRCA2* mutation carriers. Risk reducing salpingo-oophorectomy (RRSO) is estimated to reduce the risk of ovarian cancer by 80–90 % [115], although there is still a risk of primary peritoneal carcinoma, which has the same microscopic appearance and biology as epithelial ovarian cancer [116]. The clinical issues in women contemplating RRSO include the appropriate age to undergo the procedure, the extent of the surgery, and the use of hormone replacement therapy [117].

The age-specific risk of ovarian cancer in mutation carriers increases sharply after age 40, although the risk per year is still low at that age. If risk-reducing surgery is to be performed, it is reasonable to consider this between age 35 and 40. Healthy women in their 70s may still accrue a benefit from this procedure, although the absolute benefit decreases with age. Meta-analyses of RRSO among women with BRCA revealed a 50 % reduction in breast cancer incidence [118]. Breast cancer risk reduction is observed even in women who take hormone replacement therapy after surgery.

RRSO in mutation carriers should be performed by a gynecologic oncologist or other surgeon experienced in performing oophorectomy for risk reduction in high-risk women. The ovaries should be multiple-sectioned, and examined by an experienced pathologist. The fallopian tubes should be removed and carefully examined since tubal carcinomas are increased in mutation carriers. The role of

hysterectomy is less clear, as there seems to be no increased risk of endometrial cancer associated with *BRCA* mutations. Adding hysterectomy to RRSO increases per-operative risks and time to recovery slightly, however, women who wish to take tamoxifen may choose to undergo hysterectomy in order to reduce the risk of tamoxifen-associated endometrial hyperplasia [119]. Women who are planning to take estrogen may also choose hysterectomy to avoid the need for progestins. If hysterectomy would require an open procedure and tamoxifen or estrogen are not planned, it is reasonable to perform salpingo-oophorectomy alone.

The use of estrogen following RRSO is a subject of debate with no evidence that it increases the risk of breast cancer among women with BRCA mutations. RRSO in young women has been associated with increased mortality due to cardiovascular and bone effects of estrogen depletion, thus estrogen replacement therapy should therefore be strongly considered in younger premenopausal women undergoing risk-reducing oophorectomy [111, 117, 120]. Particularly if estrogen is used without progestin, breast cancer risk is still reduced after oophorectomy. One reasonable approach is to use estrogen (with progestin-containing IUD in women with a uterus) from the time of oophorectomy until around age 45–50, and then consider tamoxifen for 5 years. In general, women with a personal history of breast cancer should not take estrogen, and this decision should be made in consultation with the woman's oncologist.

31.6.8 Risk-Reducing Mastectomy

The most effective means of reducing the risk of breast cancer is with bilateral mastectomy. Since mastectomy has significant morbidity, including surgical risks and loss of sensation, options for reconstruction, the small risk of developing breast cancer in residual breast tissue, and the possibility of finding unsuspected cancer, only women at high lifetime risk (i.e., at least 30 %) of breast cancer should be offered this intervention. The seminal manuscript studied 639 women with a family history of breast cancer and found a 90 % reduction in breast cancer incidence compared with the incidence in sisters of women who did not have such surgery [121], and subsequent studies have confirmed the efficacy of this option [122, 123]. Mutation status among women in the seminal study was not known, but the reduction of risk was seen both in those with a moderate family history as well as those with a strong family history suggestive of a genetic predisposition. Most women in this series underwent subcutaneous mastectomy, a procedure that preserves the nipple-areolar complex and therefore leaves more breast tissue than a total mastectomy [124]. Options for risk-reducing mastectomy include total mastectomy, which removes the nipple-areolar complex, or total skin-sparing mastectomy in which the nipple is retained. If the latter procedure is performed, surgeons should remove as much breast tissue as possible from the underside of the nipple. A preoperative breast MRI should be performed since identifying an unsuspected cancer may alter the type of surgery that is performed, and specifically allows for cancer staging with a sentinel node biopsy.

Risk-reducing mastectomy is appropriate for some women and not for others, based primarily on the women's own beliefs and values. Many women are clear that identification of a high risk mutation would lead them to choose immediate mastectomy, and others are equally clear about their wish to avoid the procedure. For those who are undecided, several principles may assist in making a decision about this procedure.

- Prior diagnosis of breast cancer. Because not all women with breast cancer predisposition gene mutations develop breast cancer at all, some may wish to defer risk-reducing mastectomy until they are diagnosed with breast cancer, and then undergo therapeutic mastectomy on the affected side and contralateral risk-reducing mastectomy. The development of breast cancer in a woman with a *BRCA* gene mutation increases the 5-year risk of a contralateral breast cancer to around 20 %, and many women choose bilateral mastectomy at the time of diagnosis. However, most women will have a significantly greater risk of mortality from a prior breast cancer than from a breast cancer that has yet to be discovered, and the prognosis of the prior (or current) cancer should be considered in making this decision. The short- to intermediate-term risk of cancer recurrence in women with high-risk disease may be substantially higher than the risk of developing a second primary tumor. However, women with higher-risk cancers may be more likely to request bilateral mastectomy (or contralateral prophylactic mastectomy), and even if this does not improve prognosis, the procedure may provide sufficient peace of mind to be warranted.
- Risk of developing breast cancer. Most women who should consider risk-reducing mastectomy have high risk gene mutations, however given the expansion of panel testing, some women with moderate risk genes may now be considering mastectomy. Women may also wish to undergo mastectomy because of a combination of family history and personal risk factors defined by Gail [100], such as the need for prior breast biopsies based on suspicious mammograms or breast exams, and the presence of proliferative breast disease. Assuring that the woman understands her age-specific risks, as well as her lifetime risks, is also important. Although the lifetime risk of

developing breast cancer may be, for example, 70 %, a 50-year old woman has a risk that is less than that since she has already lived past some of that risk. Describing risk in quantifiable terms per year (usually around 0.5–1.5 % per year for women with mutations) may be helpful. Some women wish to undergo mastectomy because of an inflated sense of the risk of cancer, in which differentiating the age-specific and lifetime risk is useful.

- Ease of cancer detection. Breast cancer may be more or less difficult to detect, depending on the density of breast tissue on physical exam and imaging [71]. Detection is much easier in women with fatty-replaced breasts than in women with extremely dense breasts. Women may choose mastectomy over screening if screening tools are less likely to detect cancer at an early stage.
- Chemoprevention options. Risk reduction with tamoxifen or raloxifene may be an option instead of mastectomy. The degree of risk reduction in mutation carriers has not been evaluated in prospective trials, but is certainly less than with prophylactic mastectomy. Nevertheless, this option should be discussed.
- Psychological factors. Women consider prophylactic mastectomy for many reasons. For some, the family culture is to have risk-reducing surgery, and the pressure to undergo the procedure may be significant. These women should be supported if they wish to have surveillance alone. Other women have cared for family members with terminal cancer and may wish to spare their own families. Some fear developing cancer or are extremely anxious about screening, and the probability of early detection is not reassuring. All these issues should be explored in depth. Counseling or grief therapy may be appropriate in some cases. There is no absolute medical indication for this procedure, and the final decision about risk-reducing surgery is always therefore a psychological one.

31.6.9 Medical Management of Mutation Carriers Diagnosed with Breast Cancer

BRCA gene mutations have little influence on the management of breast cancer aside from decisions about breast surgery. Many women with mutations choose bilateral mastectomy if a unilateral cancer is found in order to reduce the substantial risk of developing a contralateral breast cancer. Lumpectomy with radiation therapy, however, has been demonstrated to provide good control of cancer with no increase in the risk of ipsilateral breast tumor recurrence [124].

Women who are newly diagnosed with breast cancer and judged to be testing candidates because of family history, age, or ethnicity are often required to make decisions about testing and cancer treatment simultaneously. Unless surgical treatment of the cancer itself is impacted by mutation status, there is little reason to perform testing in a woman who is not able to make a thoughtful decision about undergoing testing in a rushed situation. Test results are usually available within 2 weeks, although larger multigene panels may take longer. The major impact of genetic testing usually surgical treatment and not systemic treatment, however the use of platinum chemotherapy and PARP inhibitors to treat BRCA associated breast cancer is being investigated [125, 126]. Women with breast cancer who would choose lumpectomy over mastectomy if no mutation was found, can undergo lumpectomy, proceed with chemotherapy, and then make the decision to undergo mastectomy or post lumpectomy radiation, depending on the result of the genetic test.

31.7 Information for Extended Family Members

Although the focus of this chapter is the patient who presents with concerns about her particular family history, genetic testing is different from other medical testing in that it has implications for extended family members. Most obviously, a woman with an identifiable mutation has the chance of passing that mutation to her children, and since she almost certainly inherited it from a parent, her siblings also have a 50 % chance of having the mutation. However, extended family members can also be at risk for having the mutation, and several mechanisms, such as model letters, can be provided to patients to help them communicate with the appropriate testing candidates. Studies reveal that the majority of women share their mutation status with their families, especially with those members they believe are also at risk [127–129].

Women who do not have mutations can also provide useful information to extended family members [130]. In the case of individuals who are members of a family in which there is a known mutation, the children would have a risk of developing cancer similar to others in the general population. However, if the individual is a member of a family in which there is not a known mutation, the empiric risk information would be relevant to children, siblings, and possibly extended family members. Typically, the

responsibility to share the implications of this information is given to the patient, after appropriate education, to preserve patient confidentiality.

31.8 In Summary

As the public becomes more aware of and informed about the genetics of breast cancer, there will be an increasing demand for genetic counseling and clinical testing. Whether as part of a comprehensive clinical breast cancer clinic or as a primary practitioner's service, families at increased risk of breast cancer will be identified and should be offered appropriate services. A variety of resources from both the oncology and genetic communities are available to provide specialized care to women and their families who need genetic counseling, result interpretation, or psychological support related to testing and subsequent management decisions (Table 31.4). The future of genetic testing will be a team effort, involving the primary care physician, the cancer center and the cancer genetic service, whether it is obtaining a family and personal health history to determine the magnitude of risk, conducting genetic counseling and/or testing, or facilitating long-term medical management of the patient and her extended family members.

Table 31.4 Additional resources: websites

Facing our risks of cancer empowered (FORCE): www.facingourrisk.org. This website is a resource for individuals and families who have a strong family history of breast cancers or are carriers of a mutation that confers an increased risk of developing cancer. General information, chat rooms, a blog, and discussion board are available online, while a national meeting in May of each year allows participants to gather, and local chapters are developing in several states
National society of genetic counselors: www.nsgc.org. This site is the resource for the genetic counseling profession and contains a search function to assist consumers and professionals in finding local genetic counseling services
National institutes of health: http://www.cancer.gov/search/geneticsservices/. Cancer Net PDQ contains information about cancer, clinical trials and providers of cancer genetic services
National comprehensive cancer network: www.nccn.org. National comprehensive cancer network (NCCN) is an alliance of cancer centers and was established in 1995 to provide state-of-the-art guidelines in cancer prevention, screening, diagnosis, and treatment through excellence in basic and clinical research. This site contains practice guidelines for identification and management of genetically high-risk patients Stanford Medicine Decision Tool for Women with BRCA Mutations. http://brcatool.stanford.edu/brca.html This decision support tool is designed for joint use by women with BRCA mutations and their health care providers, to guide management of cancer risks

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