INTRODUCTION

Soon after the French revolution (1789–1799), modern scientific medicine was developed in Paris. Prominent clinician-scientists working to understand the origins of human cancer collected family histories of cancer and debated whether family clusters of cancer proved that cancer was contagious or, rather, was transmitted from parent to offspring. Writing in 1851, the pioneer of modern diagnostic pathology, Hermann Lebert, suggested that “...children come into the world carrying within them the seeds of a cancerous disease which remains latent for thirty to fifty years, but which, once developed, is fatal in the space of a few years.”¹ He recognized the value of identifying individuals with an inherited predisposition to cancer and suggested that these individuals might reduce their cancer risk by relocating to regions

KEYWORDS

- Breast neoplasms
- Gene mutation
- Cancer predisposition syndromes
- Genetic counseling
- Risk assessment
- Risk management

KEY POINTS

- Although mutations in BRCA1 and BRCA2 account for nearly 50% of the major inherited breast cancer predisposition syndromes, a variety of other high and moderate penetrance genes have been identified.
- Genetic tests that return any result other than deleterious mutation require special consideration and management.
- Professional genetic counselors serve a vital role in the cancer genetics clinic.
- Mutation carriers have several options for managing breast cancer risk, including lifestyle changes, enhanced surveillance, chemoprevention, and prophylactic surgery.
- Genetic counseling and testing should be considered in the initial evaluation of patients with newly diagnosed breast cancer. Patients need this information to make informed decisions about surgery, radiation therapy, and systemic treatments.
with a low cancer incidence. This prescient grasp of gene-environment interactions predated Gregor Mendel’s articulation of the laws of inheritance in 1865,2 Friedrich Miescher’s isolation of DNA in 1871,3 and Oswald Avery’s showing that DNA is the medium of genetic transmission in 1944.4

Although early-onset breast cancer was not linked to the D17S74 locus on chromosome 17q21 (later named BRCA15) until 1990,6 Paul Broca, a contemporary of Herman Lebert, described an apparent family with BRCA in 1866 (Fig. 1).7 He recognized that familial cancer predisposition was rare, that women were disproportionately affected with cancer compared with men, and that cancer rates in these families were at least 15 times greater than those observed in the general population.

The tenets of clinical cancer genetics articulated by Lebert and Broca in the mid-nineteenth century still hold in the twenty-first century. Specifically, major inherited predisposition syndromes account for only 5% to 10% of cases of breast cancer, women are disproportionately affected with hereditary cancer compared with men, and there is great value in identifying high-risk individuals. Ascertainment and assessment of a 3-generation family history of cancer is still the initial step in genetic risk assessment, but genetic testing provides a powerful tool for determining which individuals in a family cluster of cancer are at high risk. Individuals who are found to “carry within them the seeds of a cancerous disease” must understand the time course and magnitude of their cancer risk, the options for enhanced surveillance, and the measures that they can take to reduce their risk. For those recently diagnosed with a hereditary cancer, specific management options must be considered.

THE GENES

In healthy cells, tumor suppressor genes function to maintain DNA integrity and buffer proliferation signals. These activities slow the rate of accumulation of DNA alterations. For individuals who have inherited an altered copy of 1 of these genes, the process is accelerated and cancers develop at an increased frequency and often at an early age.

TP53 was among the first genes to be definitively associated with familial breast cancer.8 This gene is a master regulator of DNA damage repair, cell death pathways, and cell cycle control. BRCA1 was cloned in 19949 and BRCA2 in 1996.10–12 Both genes cooperate to maintain DNA integrity by facilitating error-free DNA double-strand break repair (ie, homologous recombination). BRCA1 serves a variety of other functions as well, including regulation of gene expression, cell cycle control, and regulation of protein recycling. Several genes in the Fanconi anemia pathway13 that interact with BRCA1 in homologous recombination have also been linked to breast cancer, including BARD1, BRIP1/BACH1, MRE11A, NBN, NBS1, RAD50, RAD51C, ATM, and PALB2.14–17 Other breast cancer susceptibility genes include the cell cycle

Fig. 1. A hereditary breast cancer family described by Paul Broca in 1866.7 Red circles denote women diagnosed with breast cancer, blue is liver cancer, orange gastric cancer, and green endometrial cancer. Pedigree drawn with CaGene6. (Data from Euhus DM. Cancer Gene 2012. Available at: http://www4.utsouthwestern.edu/breasthealth/cagene. Accessed February 1, 2013.)
control proteins CHEK2\textsuperscript{18} and p16\textsuperscript{19,20}, PTEN, a cytoplasmic protein that buffers proliferation signals (the way a resistor would reduce the current in an electrical circuit),\textsuperscript{21,22} CDH1 (E-cadherin), a membrane protein that links cells to other cells,\textsuperscript{23,24} and STK11 (LKB1), the Peutz-Jeghers syndrome gene, which regulates how a cell responds to proliferation signals depending on the availability of ATP.\textsuperscript{25}

**BASIC GENETICS OF INHERITED PREDISPOSITION**

Nearly all of the breast cancer predisposition genes operate in an autosomal-dominant fashion. This expression means that only 1 abnormal copy of the gene needs to be inherited from either the mother or father to significantly increase breast cancer risk. It also means that, on average, about half of the individuals in an affected family are at increased risk for cancer. Some of these genes increase risk of breast cancer more than others (ie, some have a greater penetrance). For example, in some families, a BRCA1 mutation is associated with an 80% lifetime risk of breast cancer, whereas the lifetime risk associated with a CHEK2 mutation is more in the range of 15% to 25%. In addition, mutations are rare for some of the genes, but more common for others. BRCA gene mutations account for about 50% of predisposition to inherited breast cancer, whereas each of the other genes account for fewer than 5% of these cases. The allele frequency for many of these genes varies considerably by ethnicity. For instance, BRCA1 mutations are estimated to occur in 0.06% of non-Jewish individuals, but in up to 2.6% of Ashkenazi Jewish populations.\textsuperscript{26,27} The frequency of mutated alleles for most of the other genes is lower than 0.06%. CHEK2 mutations are rare in the United States,\textsuperscript{28} but are estimated to occur in up to 1.4% of healthy Finnish individuals.\textsuperscript{29} In most cases, a significant family history of cancer is the first clue that there is a mutated gene in the family, but for some genes, such as STK11 and PTEN, new mutations are common (ie, de novo mutation). For these genes, the proband may be the first individual in the family with the syndrome. A working knowledge of mode of inheritance, penetrance, allele frequency, and de novo mutation rates is essential for consistently recognizing heritable cancer predisposition, for precisely identifying the cause, and for managing affected families. Table 1 lists the major breast cancer predisposition genes in order of penetrance.

**SINGLE-NUCLEOTIDE POLYMORPHISM PANELS**

Genome-wide association studies have identified common sequence variants that are associated with a slightly increased risk for breast cancer.\textsuperscript{30} One of the most strongly associated variants occurs in FGFR2. This variant is found in 38% of the population and is associated with a 26% increase in risk for breast cancer. This finding means an absolute lifetime risk of about 15%. There is no clinical value for identifying individuals at this risk level, but proponents of these panels assert that there is value in identifying individuals who carry multiple risk-associated single-nucleotide polymorphisms (SNPs). This view is challenged by the observations that more than one-third of women tested would be identified as increased risk, women who are homozygous for all of the risk alleles would have a relative risk for breast cancer of less than 4.0, and more than 1 million women would need to be tested to identify 1 at this risk level.\textsuperscript{31} Although these SNP panels are being marketed directly to consumers, it should be recognized that they have no clinical usefulness on an individual basis, but may have some value for population screening. In addition, although many of these SNPs have been shown to modify risk for breast cancer for carriers of the BRCA gene mutation,\textsuperscript{32,33} their role in individualized risk assessment has not yet been established.
The mutations

Table 1
Major breast cancer predisposition genes and syndromes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Risk for Breast Cancer (%)</th>
<th>Allele Frequency (%)</th>
<th>Family History and Phenotype Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1&lt;sup&gt;42&lt;/sup&gt;</td>
<td>65–81</td>
<td>0.06–1.5</td>
<td>Hereditary breast ovarian cancer syndrome: early-onset breast cancer, ovarian cancer, modest increase in male breast cancer risk</td>
</tr>
<tr>
<td>BRCA2&lt;sup&gt;42&lt;/sup&gt;</td>
<td>45–85</td>
<td>0.06–1.5</td>
<td>Hereditary breast ovarian cancer syndrome: early-onset/late-onset breast cancer, ovarian cancer, melanoma, pancreatic cancer, male breast cancer</td>
</tr>
<tr>
<td>TP53&lt;sup&gt;42&lt;/sup&gt;</td>
<td>50–80</td>
<td>&lt;0.0005</td>
<td>Li-Fraumeni syndrome: very-early-onset breast cancer, sarcoma, adrenocortical carcinoma, brain tumors, phyllodes tumor, others (many), ER-positive, PR-positive, human epidermal growth factor receptor 2-positive breast cancer</td>
</tr>
<tr>
<td>PTEN&lt;sup&gt;42&lt;/sup&gt;</td>
<td>50–85</td>
<td>0.0005</td>
<td>Cowden syndrome: breast cancer, benign and malignant thyroid disease, endometrial cancer, colorectal cancer, macrocephaly, trichilemmomas, palmar-plantar keratoses, oral mucosal papillomatosis, benign breast disease; de novo mutations 11%–48%</td>
</tr>
<tr>
<td>CDH1&lt;sup&gt;23&lt;/sup&gt;</td>
<td>39–52</td>
<td>Unknown</td>
<td>Infiltrating lobular cancer, diffuse gastric cancer with signet ring cells</td>
</tr>
<tr>
<td>STK11&lt;sup&gt;132,133&lt;/sup&gt;</td>
<td>35–50</td>
<td>0.004–0.0003</td>
<td>Peutz-Jeghers syndrome: very-early-onset breast cancer, gastrointestinal cancer, pancreatic cancer, ovarian cancer, hamartomatous polyps of the gastrointestinal tract, oral-labial pigmentation; de novo mutation rate may be as high as 50%</td>
</tr>
<tr>
<td>PALB2</td>
<td>20–30</td>
<td>0.2</td>
<td>Later-onset breast cancer, male breast cancer, pancreatic cancer</td>
</tr>
<tr>
<td>CHEK2&lt;sup&gt;134&lt;/sup&gt;</td>
<td>15–25</td>
<td>0.3–1.7</td>
<td>Similar cancer spectrum as Li-Fraumeni syndrome but lower penetrance; male breast cancer</td>
</tr>
<tr>
<td>NF1&lt;sup&gt;135&lt;/sup&gt;</td>
<td>15–25</td>
<td>0.02</td>
<td>Neurofibromatosis: early-onset breast cancer, gliomas, malignant peripheral nerve sheath tumors, café au lait spots; de novo mutations 50%</td>
</tr>
<tr>
<td>p16&lt;sup&gt;136–138&lt;/sup&gt;</td>
<td>15–25</td>
<td>Unknown</td>
<td>Familial atypical multiple mole melanoma syndrome: melanoma, pancreatic cancer, dysplastic nevi, breast cancer</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reference citations point to resources that are useful for clinical management. 

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

**THE MUTATIONS**

Fig. 2 shows the basic organization of a gene and some of the most common types of mutations. The most common deleterious mutation is an insertion or deletion of 1 or 2 nucleotides, which creates a frameshift, resulting in early termination of translation.
and a truncated protein, which can interfere with the normal functions of the full length, wild-type protein produced from the normal sister chromosome. One example is the common Ashkenazi Jewish mutation in BRCA1 known as 185delAG. This nomenclature signifies that at the 185th exonic nucleotide an AG sequence has been deleted. Although protein-truncating nonsense mutations are nearly always deleterious, other exonic mutations such as point mutations that change 1 amino acid (ie, missense mutations), point mutations that do not change any amino acids (ie, synonymous mutations), and in-frame insertion or deletion of entire triplets may or may not be deleterious. Promoter region and intronic mutations can also be deleterious. This situation is especially true for mutations that occur near the beginning or end of an intron, where they may interfere with subsequent mRNA splicing. An example of 1 such mutation is BRCA1 IVS4+1G>T, which means that the first nucleotide of intervening sequence 4 (ie, the fourth intron) has been changed from a G to a T. Other intronic mutations and promoter region mutations may be deleterious if they affect regulatory regions.

**VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE**

Although most frameshifting and nonsense mutations generate truncated proteins that interfere with cellular functions and increase cancer risk, disease association is uncertain for many of the single-nucleotide alterations shown in Fig. 2. For BRCA1 and BRCA2, it is estimated that 2.9% of identified mutations fall into this latter category. This is a significant improvement over the 7% to 15% rate previously reported. Variants of uncertain clinical significance (VUS) rates are higher for non-White populations, but have declined from 22% to 46% to 2.6% to 7.8% in recent years. Work is continually ongoing to definitively classify these variants as deleterious or nondeleterious.
From a clinical perspective, patients need to know at the outset that their genetic test may return a VUS. These individuals may need to be managed the same as any individual with a noninformative negative gene test (see later discussion). A record of the genetic test result and patient contact information needs to be maintained so that these individuals can be contacted when the VUS is classified as deleterious or nondeleterious.

FOUNDER MUTATIONS

Sometimes, during the course of human migration and colonization, small populations of individuals harboring specific mutations become geographically or socially isolated. After many generations of relative isolation, these mutations can become common in the population. The 3 BRCA Ashkenazi founder mutations, BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT, are examples of this situation. It is postulated that mass migration of Spanish Jews to the Americas in 1492 accounts for the high prevalence of Ashkenazi Jewish founder mutations observed in Hispanics. Because these 3 founder mutations account for about 90% of BRCA gene mutations in the Ashkenazi Jewish population, genetic testing usually begins with this 3-gene panel in these individuals.

GENETIC TESTS

Germline genetic testing is performed on DNA isolated from leukocytes obtained from a venous blood sample or from oral epithelial cells obtained from a saliva sample. If the intent is to test for 1 or a few specific mutations (eg, single-site tests), only limited regions of the gene of interest are assessed. If a more general screen for mutations is desired, DNA sequencing reactions are designed to assess portions of the promoter, some or all of the exons, and sections of the introns that may be involved in messenger RNA (mRNA) splicing. The clinically relevant point is that gene tests are rarely capable of identifying every possible deleterious mutation in a gene. In addition, an idiosyncrasy of the sequencing technology in common use is that it generates a normal read-out if there are rearrangements, duplications, or deletions affecting 1 or more exons. Special testing to identify the 5 most common large rearrangements frequently observed among individuals of European ancestry was added to routine BRCA testing beginning in 2002, but this is a candidate approach that does not identify large rearrangements that are not specifically looked for. Myriad Genetics (Salt Lake City, UT), the primary provider of BRCA gene mutation testing, offers an additional test, called the BRACAnalysis Large Rearrangement Test (BART), which provides a more comprehensive test for rearrangements in BRCA1 and BRCA2. Whether this test is routinely performed or not after a negative BRCA sequencing test is dependent on the personal and family history of cancer (eg, a BRCAPRO mutation probability >30% usually triggers the reflex protocol). For individuals who do not meet the established criteria for BART testing, the test must be ordered and paid for separately. These large rearrangements account for up to 17% of deleterious BRCA gene mutations in individuals of Near-East/Middle-Eastern ancestry and up to 22% for individuals with Latin-American/Caribbean ancestry.

Currently available gene tests are not capable of identifying every deleterious mutation, and testing protocols continue to evolve, making it essential that patients with noninformative negative gene tests remain accessible for retesting as technologies change. The sensitivity of BRCA gene testing is estimated at 80% to 90%. Extended testing may be indicated depending on the family history and ethnic background of the
counselee. A negative test must be carefully interpreted in light of all available information.

THE NONINFORMATIVE NEGATIVE GENE TEST

The positive gene mutation test poses few difficulties in interpretation and should initiate the risk assessment and intervention activities described later. Every negative test requires special consideration and interpretation. Maternal and paternal lineage must be considered separately in the interpretation of a negative test. If the cancer predisposition is clearly resident in only 1 lineage, and this predisposition has been adequately explained by the presence of a mutation in 1 or more relatives of that lineage, then a negative gene test is highly informative and the counselee can be reassured that their cancer risk is likely no greater than that of the general population. When all of these criteria are not met, the test result is classified as noninformative negative. Each of the following issues must be addressed for every patient with a noninformative negative test result: could the counselee have inherited an identifiable gene mutation from the other side of the family? Could the gene test have missed a deleterious mutation (ie, is more extensive testing indicated)? Should a different gene be tested? The decision to test other genes can be guided by the family history and phenotype clues listed in Table 1. If a noninformative negative gene test cannot be resolved, then the patient must be managed as though they are at increased risk for the cancers associated with the most likely syndrome suggested by the family history.

The best approach for minimizing noninformative negative gene tests is to always test the individual in the family who is most likely to carry a mutation. This is frequently not the individual who is presenting for genetic risk assessment. Every effort should be made to identify and engage the relative with the greatest mutation probability. When family dynamics or early deaths from cancer preclude this strategy, the counselee should be thoroughly educated concerning the likelihood and implications of a noninformative negative test.

PROFESSIONAL GENETIC COUNSELORS

In 2012, the American College of Surgeons Commission on Cancer accreditation program (http://www.facs.org/cancerprogram/index.html) mandated that cancer risk assessment, genetic counseling, and genetic testing services be provided to patients by a qualified genetic professional either on site or by referral. Practice guidelines for genetic counselors have been well articulated by the National Society of Genetic Counselors. Essential services performed by professional genetic counselors include pretest and posttest counseling and education; interpretation of negative results, which often requires decisions about carrying out more extensive testing, or testing other genes; maintaining patient contact files so that when new gene tests become available or variants of uncertain significance are reclassified the affected patients can be notified; helping newly identified mutation carriers to notify their family members; and aggressively pursuing government, industry, or philanthropic funding to cover the costs of genetic testing for the uninsured or underinsured. These activities are beyond the scope of the average clinical practice. Board-certified professional genetic counselors are essential for the operation of cancer genetics programs.

IDENTIFYING MUTATION CARRIERS

Genetic testing is expensive and the results can have significant psychosocial impacts; consequently, testing is currently offered selectively. The most pragmatic
criteria for offering testing include: (1) the individual is reasonably likely to carry a mutation, (2) the test result would influence health care decisions for the counselee or the counselee’s relatives, and (3) there is some mechanism available for paying for the test. The last criterion automatically creates a socioeconomic disparity for the use of cancer genetics services and places third-party payers in the position of defining “reasonably likely to carry a mutation.” Guidelines for recommending genetic testing have been published for most of the known hereditary breast cancer syndromes and many, but not all, insurers follow these. The National Comprehensive Cancer Network (NCCN) regularly publishes updated guidelines for several of the syndromes.

Recognizing individuals with a hereditary predisposition to breast cancer usually requires collection and thoughtful evaluation of a 3-generation cancer family history. Early-onset breast cancer is the hallmark of many of the syndromes, but the occurrence of certain combinations of cancers in a family regardless of age at onset may also provide a clue (see Table 1). For syndromes with a high de novo mutation rate (eg, Cowden syndrome and Peutz-Jeghers syndrome), the family history may not be helpful, but an astute clinician recognizes the associated phenotypic features on physical examination (see Table 1).

Mathematical models such as BRCAPRO, BOADICEA, and Tyrer-Cusick can be used to calculate the probability of a BRCA gene mutation. CancerGene is a widely used desktop program that uses BRCAPRO to estimate mutation probabilities and cancer risks. An online program for calculating the probability of a PTEN mutation is available for patients with suspected Cowden syndrome. Mathematical models are neither sensitive nor specific enough to define a specific mutation probability threshold lower than which genetic testing can be safely avoided, but these models can enhance the accuracy of risk estimations for genetic counselors, and the graphical outputs are useful for risk counseling.

Traditionally, family history screening and referral for genetic counseling have been the responsibility of primary care physicians. These physicians are already overburdened, so it is not surprising that detailed cancer family history screening is not routinely practiced. An alternative approach is to screen large populations of women through mammography departments using brief, validated family history tools. In addition, the recognition that 10% to 25% of women diagnosed with triple-negative breast cancer before the age of 50 years carry a BRCA gene mutation provides a way of engaging pathology departments for hereditary breast cancer screening. Ideally, health care providers at all levels would consistently collect detailed cancer family histories and recognize patterns suggesting an inherited predisposition. At a minimum, the single-individual phenotypes listed in Table 2 should be widely recognized and should prompt cancer genetics referrals.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>BRCA Mutation Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double primary breast-ovarian cancer</td>
<td>86</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>8–25</td>
</tr>
<tr>
<td>Breast cancer in an Ashkenazi Jewish woman</td>
<td>~15</td>
</tr>
<tr>
<td>Triple-negative breast cancer &lt;60 y of age</td>
<td>10–25</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>10–15</td>
</tr>
<tr>
<td>Female breast cancer &lt;45 y of age</td>
<td>~10</td>
</tr>
</tbody>
</table>
MANAGING RISK FOR PRIMARY BREAST CANCER IN THOSE WHO TEST POSITIVE

A positive gene test permits proactive development and execution of a plan to reduce cancer risk or to diagnose cancer at an early more easily managed stage. Consequently, the initial task after receiving a positive result is to quantify the cancer risk over time. Lifetime breast cancer risk ranges from 65% to 81% for BRCA1 mutation carriers and 45% to 85% for BRCA2 carriers. The mean age at diagnosis of breast cancer is about 44 years for BRCA1 mutation carriers and 47 years for BRCA2 carriers, but age at onset varies by family, particularly for BRCA2 families. Some genes, such as TP53 and STK11, are associated with very-early-onset breast cancer, whereas genes like CHEK2 and PALB2 are associated with later-onset breast cancer. In some families, the mutated gene is highly penetrant (ie, most or all of the mutation carriers develop cancer), whereas in other families, gene-gene and gene-environment interactions reduce the cancer risk. A careful assessment of the 3-generation cancer family history in conjunction with the model calculations described in the preceding is helpful at this juncture. Obtaining a sense of the penetrance of the gene mutation in a specific family is particularly helpful for the low or moderate penetrance genes shown in Table 1.

MODIFIERS OF RISK

All BRCA gene mutation carriers are at significantly increased risk for breast cancer, but certain genetic, reproductive, and lifestyle factors can modify this risk. For instance, the Ashkenazi Jewish founder mutation, BRCA2 6174delT, is associated with lower lifetime breast cancer risk (about 55%) compared with other mutations. In addition, several SNPs that are known to slightly increase the risk for sporadic breast cancer have been shown to modify risk in BRCA gene mutation carriers. Late age at menarche, early age at first live birth, and increasing numbers of live births have been shown to reduce the risk of sporadic breast cancer. Menarche at or after age 14 years has been associated with a 54% reduction in breast cancer risk for BRCA1 mutation carriers, however, early age at first live birth does not seem to reduce risk for breast cancer for BRCA gene mutation carriers. Pregnancy has a minimal effect on risk for breast cancer for BRCA1 mutation carriers, but each pregnancy increases risk by 17% for BRCA2 carriers. Lactation for more than 1 year reduced breast cancer risk by 40% for BRCA1 mutation carriers, but did not seem to have an effect in BRCA2 carriers. Combined hormone replacement therapy (cHRT) is known to increase the risk for sporadic breast cancer. One study has suggested that cHRT does not increase risk in BRCA1 mutation carriers, whereas estrogen-only therapy reduced risk by 49%. Caffeinated coffee is believed to provide antioxidant effects. Consumption of 6 or more cups of caffeinated coffee per day was associated with reduced risk for breast cancer among BRCA1 mutation carriers. Weight gain in adulthood and energy consumption, but not other dietary factors, have been associated with increased risk for breast cancer in BRCA gene mutation carriers. There is evidence that medical radiograph exposure (eg, chest radiographs) before the age of 20 years may increase future breast cancer risk for BRCA gene mutation carriers. The risks of yearly mammography before age 30 years should be carefully considered.

DEVELOPING AN INDIVIDUALIZED RISK MANAGEMENT STRATEGY

The primary options for managing cancer risk in those who test positive include enhanced surveillance, chemoprevention, and prophylactic surgery. The relative
benefits and risks of each of these choices are explained to the patient in detail. Consideration is given to the specific cancer family history, including apparent penetrance and ages at diagnosis, and an understanding is sought of the patient’s unique psychosocial perspective, risk tolerance, and family and career goals. Management plans are individualized. There are no hard and fast rules governing what must be done and when. The role of the clinician is to help the well-informed patient develop a personally acceptable plan and then to engage the appropriate multidisciplinary team to execute this plan.

ENHANCED SURVEILLANCE

The sensitivity of screening magnetic resonance imaging (MRI) for detection of breast cancer in high-risk women ranges from 71% to 94% compared with 33% to 59% for mammography.\(^{67–72}\) Screening MRI is less specific than mammography, so its use increases the rate of benign breast biopsies (about 10% for the first MRI); but this rate decreases with successive rounds of screening. Screening sonography has a sensitivity of 17% to 65%\(^{69–71}\) and occasionally identifies a cancer missed by mammography and MRI. Adding modalities to the screening algorithm incrementally increases the cancer detection rate, but also increases the benign biopsy rate. The primary role of sonography is in the further characterization of mammographic or MRI lesions, but the introduction and validation of automated screening sonography platforms may force a reassessment.\(^{73}\) The combination of clinical breast examination, screening mammography, and screening MRI has a sensitivity of 86% to 94% for detection of breast cancer among BRCA gene mutation carriers.\(^{68,69}\) The NCCN has recommended that BRCA gene mutation carriers begin practicing breast self-examination at the age of 18 years and twice-yearly clinical breast examination, with yearly screening mammography and MRI beginning at the age of 25 years.\(^{42}\) Yearly mammography before the age of 30 years may increase risk for breast cancer in BRCA gene mutation carriers, so this recommendation should be reconsidered. The American Cancer Society supports screening MRI for anyone with a lifetime breast cancer risk greater than 20%, making it a reasonable option for most of the syndromes shown in Table 1.\(^{74}\) The age when screening begins may be adjusted according to the earliest age at diagnosis of breast cancer in the family. A common practice is to begin screening 10 years before the earliest age at diagnosis of breast cancer in the family and to stagger the mammography and MRI by 6 months to reduce the screening interval.

CHEMOPREVENTION

Tamoxifen reduces the risk of breast cancer by nearly 50%, even for women with up to 3 first-degree relatives with breast cancer.\(^{75}\) Tamoxifen has not been prospectively studied in women with deleterious BRCA gene mutations, but an analysis of 19 mutation carriers included in the NSABP P1 Breast Cancer Prevention Trial suggested a 50% reduction in risk for BRCA2 mutation carriers but no effect for BRCA1 carriers.\(^{76}\) This finding is not unexpected, because tamoxifen reduces the risk only for estrogen receptor (ER)-positive breast cancer; and, whereas 60% to 75% of BRCA2-associated breast cancers are ER-positive, 70% to 90% of BRCA1-associated breast cancers are ER-negative.\(^{77–79}\) Tamoxifen is FDA-approved by the US Food and Drug Administration (FDA) for prevention of breast cancer in women aged 35 years or older. Given the early age at onset of breast cancer in BRCA gene mutation carriers, the modern trend for delayed childbirth, and uncertainty concerning the impact of tamoxifen on lifetime risk, tamoxifen is used only infrequently (6%)
among BRCA mutation carriers.³⁸ Raloxifene, which is FDA-approved for postmenopausal women only, is used even less frequently (3%).

**PROPHYLACTIC BILATERAL SALPINGO-OOPHORECTOMY**

Bilateral salpingo-oophorectomy (BSO) reduces the incidence of primary ovarian cancer in BRCA gene mutation carriers by 80% to 96%; however, special care must be taken to remove the entire fallopian tube (which is believed to be the origin of many BRCA gene-mutation associated ovarian cancers), and systematic protocols should be followed in the operating room and pathology laboratory to identify occult ovarian cancer.³⁵,³⁶ Premenopausal BSO reduces breast cancer risk by about 50%.³¹,³⁷³⁸ It is not clear whether postmenopausal BSO also reduces breast cancer risk, but its effects on circulating androgen levels are of interest in this regard.³⁹ Most BRCA2 gene mutation-associated breast cancers are ER-positive, so it is not surprising that BSO reduces breast cancer risk by 64% to 72% in these women.⁹⁰,⁹¹ Prophylactic BSO also reduces breast cancer risk in BRCA1 gene mutation carriers, but only by 37% to 39%.⁹⁰,⁹¹ Early, abrupt surgical menopause is associated with disabling quality of life issues in some women.⁹² Hormone replacement therapy does not seem to interfere with the risk-reducing effects of BSO and should not be withheld if required. The NCCN guidelines recommend risk-reducing BSO for BRCA gene mutation carriers between the ages of 35 and 40 years.⁴² The impact of BSO on risk for breast cancer should not be overestimated for BRCA1 mutation carriers.

**BILATERAL PROPHYLACTIC MASTECTOMY**

Bilateral prophylactic mastectomy (BPM) reduces breast cancer risk by more than 90%,⁹⁴–⁹⁶ but 1 year later, 48% of women report feeling more self-conscious and less sexually attractive primarily because of visible scars.⁹⁷ Nipple-sparing mastectomy (NSM) provides excellent cosmesis, and the scars can be well hidden by using lateral inframammary incisions (Fig. 3). Some have suggested that NSM leaves considerable breast tissue behind and should be avoided in BRCA gene mutation carriers.⁹⁸ One of the earliest BPM series (90% of which were NSM) included 214 genetic high-risk women and reported no primary breast cancers among the 26 confirmed BRCA gene mutation carriers after a median follow-up of 13 years.⁹⁹ A recent review of NSM supports the oncologic safety of the procedure and suggests that the risk of cancer in the retained nipple is less than 1%.¹⁰⁰ When NSM is performed correctly, the areolar flap is thin relative to the more peripheral flaps. Breast epithelial structures can extend close to the dermis of the breast skin, but terminal duct lobular units are only infrequently identified in excised nipples.¹⁰² Consequently, the volume of residual breast tissue is most related to the area of retained skin and the thickness of the flaps. The nipple-areolar complex accounts for only a tiny fraction of this volume. Patients should be advised that available evidence suggests excellent risk reduction with NSM, but that, theoretically, the risk can be reduced further by taking more skin. Lifetime risk for breast cancer after BPM is estimated at 7% for BRCA gene mutation carriers.⁹⁸

**MANAGING CANCER RISK IN MEN**

Lifetime breast cancer risk is estimated at 1.8% for men with BRCA1 mutations and 8.3% for BRCA2.¹⁰³ Mutations in CHEK2 PALB2, and PTEN are also associated with an increased risk for male breast cancer. Men who carry BRCA2 gene mutations
are at increased risk for a variety of other cancers, but the absolute risk for common cancers such as prostate, pancreatic, and melanoma do not seem to justify enhanced surveillance. However, BRCA2 gene mutation carriers are at risk for aggressive, early-onset prostate cancer, which is associated with a higher mortality than sporadic prostate cancer. Screening for breast, prostate, and pancreatic cancer is practiced in some centers. The NCCN guidelines recommend training in breast self-examination, clinical breast examination every 6 months, and consideration of baseline mammography. Our practice is to encourage breast self-examination, begin annual clinical examination and mammography at age 30 years, and annual prostate examination and prostate-specific antigen measurements at age 40 years.

Fig. 3. This 24-year-old woman presented with a clinical diagnosis of Peutz-Jeghers syndrome based on a history of intussusception caused by small intestinal hamartomatous polyps at the age of 3 years. Family history was positive for fallopian tube cancer in a maternal aunt (BRCA1/2-negative) and breast cancer in her maternal grandmother. (A) Note the lip pigmentation. (B) Her first screening mammogram showed a cluster of pleomorphic calcifications (yellow circle) diagnosed as ductal carcinoma in situ on core biopsy. (C) She underwent bilateral total NSM, and this image shows the postoperative result.
MANAGING BREAST CANCER IN MUTATION CARRIERS

Breast cancers that arise in the context of a deleterious BRCA1 or BRCA2 gene mutation have unique biologic features that directly affect surgical decisions, radiation therapy options, and the choice of systemic agents. Gene mutation testing should be part of the initial evaluation of patients with newly diagnosed breast cancer who are reasonably likely to carry a mutation based on the criteria described in the preceding sections. A thorough review of preoperative genetic testing and the treatment implications has been published recently.107

BREAST CANCER OUTCOME

Published data comparing breast cancer–specific and overall survival for BRCA gene mutation-associated and sporadic breast cancer are inconsistent, but generally suggest no difference.108,109 A recent meta-analysis reported that 5-year progression-free (ipsilateral breast and distant sites) and overall survival are significantly reduced in BRCA1 mutation carriers, but not BRCA2 carriers,110 whereas a recent international population-based cohort study found that distant recurrence and mortality were higher for BRCA2, but not BRCA1-associated cancers.111

BREAST-CONSERVING SURGERY VERSUS MASTECTOMY

Breast conservation in BRCA gene mutation carriers is associated with the same regional and distant recurrence rates and the same breast cancer–specific and overall survival as mastectomy.108,109 However, BRCA gene mutation carriers considering breast conservation must understand that ipsilateral breast tumor recurrence (IBTR) rates generally range between 1.7% and 2.7% per year,109,112 but can be as high as 4% per year for very-early-onset breast cancer (eg, age 42 years or younger).113 Systemic adjuvant chemotherapy seems to reduce this risk.109 BRCA gene mutation-associated breast cancer is classified as “Unsuitable for accelerated partial breast irradiation outside of a clinical trial,”114 but available data suggest that side scatter from whole breast radiation therapy does not increase risk for contralateral breast cancer.109,113

Risk for contralateral breast cancer, which ranges from 2.0% to 6.2% per year,108 should also be considered when making initial surgical decisions. This risk is higher for younger women (eg, <50 years) and for women with 2 or more first-degree relatives with breast cancer.115 Retrospective data suggest that bilateral mastectomy may be associated with improved breast cancer–specific survival for younger women (eg, <50 years) with hormone receptor negative breast cancer,116 and for women with family histories of breast cancer.117

BSO

All BRCA gene mutation carriers should consider BSO as an option for reducing ovarian cancer risk, but its value in patients who have newly diagnosed breast cancer is unclear. For example, a recent study that included 302 cases of breast cancer from 9 centers reported that BSO did not significantly reduce the rates of IBTR, contralateral breast cancer, or distant recurrence.109 Conversely, a PROSE (Prevention and Observation of Surgical Endpoints) study that included 1060 patients with BRCA mutation-associated breast cancer reported that, although BSO did not reduce the risk of second primary breast cancers, it was associated with a reduction in breast cancer–specific and all-cause mortality.90
CHEMOTHERAPY DECISIONS

BRCA1 gene mutation carriers treated with anthracycline-based neoadjuvant chemotherapy experience pathologic complete response (pCR) rates that are similar to or greater than those observed among sporadic cases, but responses in BRCA2 patients are more variable.\textsuperscript{118–120} Taxanes are among the most commonly used agents for chemotherapy of breast cancer. However, there is evidence that BRCA1-mutated triple-negative breast cancer is highly resistant to docetaxel in the metastatic setting\textsuperscript{121} and lower than expected response rates have been observed for both ER-positive and ER-negative BRCA1 mutation-associated breast cancer in the neoadjuvant setting.\textsuperscript{122} Until recently, platinum agents were rarely used in breast cancer. Cell-line data suggest that resistance to paclitaxel is directly correlated with sensitivity to cisplatin,\textsuperscript{123} and loss of BRCA1 is associated with cisplatin sensitivity.\textsuperscript{124} One retrospective study of neoadjuvant chemotherapy that included 102 BRCA1 patients reported a 20% pCR rate for anthracycline-based regimens compared with 83% to 90% for cisplatin.\textsuperscript{125,126}

TARGETED THERAPY

Inhibitors of poly (adenosine diphosphate-ribose) polymerase (PARP) block DNA single-strand break repair. Unrepaired single-strand breaks are converted to double-strand breaks during DNA replication. BRCA-mutated cells are deficient in DNA double-strand break repair, rendering them highly sensitive to PARP inhibitors. An early phase 1 trial of the oral PARP inhibitor, olaparib, in patients with advanced, treatment-refractory cancers observed objective responses in BRCA mutation carriers only, including 1 durable complete clinical response in a patient with breast cancer.\textsuperscript{127} A second phase 1 trial restricted to advanced or metastatic breast cancer in BRCA gene mutation carriers recorded a 50% objective response rate for BRCA1 carriers compared with 22% for BRCA2 carriers at the 400-mg twice-daily dose.\textsuperscript{128} PARP inhibitors are not approved by the FDA for the treatment of breast cancer, but there are more than a dozen clinical trials open and accruing that target BRCA mutation carriers, many of which include PARP inhibition (ClinicalTrials.gov).

THE FUTURE OF GENETIC TESTING

The preceding sections describe careful assessment of a 3-generation family history of cancer and attention to phenotypic clues to identify individuals who may have a hereditary predisposition to breast cancer and to determine which gene or genes to test. With the introduction of massive parallel sequencing (ie, next-generation sequencing), it is becoming technically and economically feasible to simultaneously screen large numbers of genes for point mutations, rearrangements, duplications, and deletions.\textsuperscript{129,130} These tests are already commercially available (eg, Breast-Next\textsuperscript{\textregistered}131), but patent issues exclude BRCA1 and BRCA2. As the cost of these tests diminishes and more genes are added, it is possible that comprehensive genetic testing will become as commonplace as lipid testing for cardiovascular risk assessment. In addition, exome sequencing is increasingly performed for a variety of conditions unrelated to cancer. These screens can surreptitiously identify mutations in breast cancer predisposition genes. Interpreting these test results for patients will impose a heavy burden on cancer genetics professionals because many new variants of uncertain clinical significance will be identified, most of the genes included in these panels have low or moderate penetrance, and there are not enough data to rationally formulate risk management strategies for moderate penetrance mutations.
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