Considerations in Testing for Inherited Breast Cancer Predisposition in the Era of Personalized Medicine

Benjamin Powers, MD[a], Tuya Pal, MD[b], Christine Laronga, MD[a,*]

KEYWORDS

- Inherited breast cancer syndromes • Surgical considerations
- Personalized medicine • Germline mutation

KEY POINTS

- Multigene panel testing has led to an increase in the number of individuals (both affected and unaffected by cancer) being identified with a germline mutation (ie, pathogenic variant).
- Surgeons are often at the forefront of point of service for individuals at risk for inherited cancer syndromes and must stay current with identifying these at-risk individuals.
- Provision of care through a multidisciplinary team, inclusive of genetic counseling before and after testing, is imperative to appropriately counsel and manage individuals with inherited cancer syndromes.
- Surveillance and management of individuals is personalized based on the gene in which the pathogenic variant is identified, often in conjunction with the personal and family cancer history.

INTRODUCTION

Breast cancer remains the most common cancer and the second leading cause of death affecting women in 2017.[1] Women in the United States have a 12% lifetime risk of developing breast cancer,[2] with an increase in breast cancer incidence from 2004 to 2013, exclusively caused by increasing rates among nonwhite women.[3]

Studies of families have shown that the risk of breast cancer increases with the number of affected relatives.[4] Although most breast cancers are sporadic, 5% to

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[a] Department of Breast Oncology, H. Lee Moffitt Cancer Center, 10920 N. Mckinley Drive, Tampa, FL 33612, USA; [b] Department of Medicine, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
* Corresponding author.
E-mail address: christine.laronga@moffitt.org

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10% of cases are caused by a germline mutation (which may also be referred to as a pathogenic variant) in an inherited cancer gene leading to hereditary cancer predisposition.[5] Mutations in these genes lead to a significantly higher risk of developing breast and other cancers compared with cancer risks among women with sporadic breast cancer.[6]

Over the last few years, important technological advances realized through next-generation sequencing (NGS) technologies coupled with the loss of the ability to patent genes have led to greatly decreased costs for genetic testing. NGS-based tests have led to paradigm shifts in genetic testing, enabling clinicians to test for multiple conditions simultaneously (called multigene panel testing) compared with the prior phenotype-directed approaches with sequential testing of 1 condition at a time through the use of Sanger sequencing. With the increasing use of multigene panel tests, the genetic counseling and testing landscape has continued to rapidly evolve. Furthermore, with the identification of more high-risk individuals, the hope is that this information may be leveraged to improve cancer outcomes and influence evidence-based screening, diagnosis, and treatment of patients with breast cancer. Despite the considerable technological advances in genetic testing, the surgical clinic remains the primary locus for identification and management of many of these high-risk patients.[7] However, lack of identification coupled with barriers in access and use of genetic services remain significant challenges to achieving equity through risk reduction strategies.[8,9] Furthermore, many busy surgeons lack the time needed to appropriately counsel patients regarding risk assessment, testing, and results interpretation, and some also have limited proficiency and lack formal training in genetics. These factors may lead them to recommend prophylactic surgery regardless of the gene in which the pathogenic variant (or even a variant of uncertain significance [VUS]) is encountered.

This article focuses on identification of individuals at high risk for inherited breast cancer and referral to (and/or conduct of) genetic counseling and testing for hereditary cancer syndromes, if appropriate. Referral in the context of a newly diagnosed patient with breast cancer or a suspected unaffected high-risk patient for further genetic evaluation is outlined. In addition, approaches for management of specific moderate-penetrance to high-penetrance hereditary breast cancer syndromes are reviewed.

IDENTIFICATION OF HIGH-RISK INDIVIDUALS

Identification of high-risk individuals is predicated on knowledge of the extent and magnitude of breast cancer risk factors and is a multistep process involving a multidisciplinary team of health care professionals. Multiple associations and societies have produced recommendations for screening for genetic predisposition to cancer. Based on recommendations from the National Comprehensive Cancer Network (NCCN), US Preventive Services Task Force, and the National Accreditation Program for Breast Centers (NAPBC), individuals at high risk for hereditary cancer should be offered genetic counseling.[10–12] Although the definition of high risk carries a subjective component, because patients may interpret personal risk differently, there remains an onus on clinicians to provide patients with an accurate assessment of risk to best equip the patients in the informed decision-making process.

The starting point in surgical practice for identification of high-risk (genetic and nongenetic) individuals is the clinical history and physical examination (**Table 1**). Clinical history should include a 3-generation family pedigree of any cancer occurrence and age at diagnosis, inclusive of both the maternal and paternal lineage, as well as all relatives given that family structure is also an important consideration when

Table 1
Indications for genetic counseling referral

Personal History		Personal + Family History Risk Factors		Family History Risk Factors
No history: Breast cancer				with known mutation in a cancer susceptibility gene in family
			or	≥ 2 Breast cancer primaries in same individual
			or	≥ 2 Breast cancer primaries same side of family with 1 person diagnosed <50yrs
			or	1st/2nd degree relative with Breast cancer <45yrs
			or	family history of Ovarian cancer
			or	Male Breast Cancer
			or	≥3 of the following cancers in any combination: breast, colon, kidney, pancreatic, prostate, melanoma, sarcoma, adrenocortical, brain tumors, leukemia, diffuse gastric cancer, endometrial, thyroid
		Personal History of Ovarian cancer		
		Personal History of Pancreatic cancer		and Ashkenazi Jewish ancestry
			or	1 Breast cancer ≤50yrs
			or	1 Ovarian cancer
			or	1 Pancreatic cancer
		Personal History of 2 of these (1 <45yrs): sarcoma or brain tumor or leukemia or lung bronchoaveolar		
		Personal history of adrenocortical cancer		
		Large head circumference and: thyroid cancer or endometrial cancer or multiple GI harmatoma polyps or mucocutaneous lesions		
History: Breast cancer	if:	with known inherited gene mutation		
	or	Breast cancer <50yrs (Triple Negative Cancer <60yrs)		
	or	2 Breast cancer primaries in same person		
	or	Pancreatic cancer any age		
	or	Male Breast cancer		
Any Age if:		1. Ashkenazi Jewish ancestry or	or	≥1 close relative with Breast cancer ≤50yrs or Ovarian Cancer any age
		2. personal history of: pancreatic, prostate, melanoma, sarcoma, adrenocortical, leukemia, diffuse gastric cancer, colon, endometrial, thyroid, kidney	or	≥3 of the following cancers in any combination: breast, pancreatic, prostate, melanoma, sarcoma, adrenocortical, brain tumors, leukemia, diffuse gastric cancer, colon, endometrial, thyroid, kidney
			or	≥2 close relative with Breast cancer and/or Pancreatic cancer any age

determining risk. Identification of breast cancer in a first-degree relative nearly doubles the risk in an individual and has been observed in approximately 13% of patients with breast cancer. The elements of risk factors for breast cancer span across categories of demographic, reproductive, and biological, and environmental risk factors (**Table 2**). Because most breast cancers are hormone receptor positive, many of these risk factors are hormonally driven.

The timeline for patient referral for genetic counseling is based on the clinical context. Undiagnosed patients who present with symptoms or signs of breast cancer should first undergo appropriate steps for diagnosis of cancer, including imaging studies and tissue biopsy. Once a cancer diagnosis has been made, the timeline to

Table 2
Elements of breast cancer risk

Category	Factor	Comments
Demographics	Female sex	
	Increasing age	
Ethnicity/race	White	Increased incidence of *BRCA1*/*BRCA2* mutations in Ashkenazi Jewish descent
BMI*	Obesity	Postmenopausal: all races/ethnicities
	Obesity	White: any age
Reproductive history*	Younger age at menarche	Age <11 y
	Lower parity	Nulliparous: highest risk
	Age at first live birth	Age >30 y
	Age at menopause	Older
Exogenous factors*	Estrogen/progestin therapy	Current or past; especially combination use >10 y
	Alcohol consumption	Weekly, >3 servings
Miscellaneous	Genetic predisposition	
	Prior thoracic radiation	<30 y of age
	Prior breast biopsy with mammary dysplasia	Lobular carcinoma in situ, atypical ductal hyperplasia, atypical lobular hyperplasia, flat epithelia atypia
	Prior breast biopsies	Risk increase with number of biopsies; cyst aspiration not included
	Breast density	

Abbreviation: BMI, body mass index.

refer for genetic counseling and consider testing becomes short, because this information may contribute to surgical decision making. If the patient has no evidence suggestive of breast cancer, it still remains important to identify and offer the patient a nonurgent genetic counseling referral, given that the results may alter the clinical surveillance and management of the patient (ie, through early detection or prevention of cancer).

Given the wide variation in magnitude of cancer risk as well as cancer spectrum based on the gene in which a mutation is identified, the American Society of Clinical Oncology has consistently used 3 criteria since 1996 for proceeding with genetic testing[1]: the individual has a personal or family history suggestive of a cancer genetic susceptibility condition,[2] the test can be adequately interpreted, and[3] the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members.[13] Although these criteria were developed at a time when testing was limited to 1 or 2 genes, they have become increasingly important because multigene panel testing is becoming the norm in many practices, leading to complex conversations with patients regarding management strategies if a pathogenic variant is identified. Keeping abreast of all of the inherited breast cancer genes and their respective cancer spectra contained within the various multigene panels is a challenge to most practicing surgeons. This challenge has made it even more imperative for surgeons to become familiar with the criteria for referral for genetic counseling and testing.

Among patients without a personal history or current diagnosis of breast cancer, several familial risk stratification tools are available to determine the need for in-depth genetic counseling, including the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and

FHS-7.[12] The US Preventive Services Task Force listed these tools as clinical predictors to determine which women should undergo referral for genetic counseling because of increased risk for *BRCA* mutations.[11] Furthermore, they recommend against general breast cancer risk assessment models such as the National Cancer Institute Breast Cancer Risk Assessment Tool (based on the Gail model), which are not designed to stratify based on inherited risk in order to identify those who should receive genetic counseling or *BRCA* testing. The NCCN also has criteria for appropriate referrals for further genetic evaluation according to personal risk factors, personal and/or family history risk factors, and family history risk factors.[10]

GENETIC COUNSELING

The National Society of Genetic Counselors (NSGC) has enumerated several components of genetic counseling.[14] Broadly, the aim of genetic counseling is to discuss the benefits, limitations, and risks of genetic testing. This process involves communicating often complex biomedical and statistical issues at the core of genetic testing into a language that patients can understand. This dialogue forms the foundation for the patients to make informed decisions about proceeding with genetic testing and management of risk in their health care. In addition, the counseling process serves to describe the link between testing options for cancer and the goals of early detection and management. The NCCN guidelines highly recommend both pretest and posttest counseling when results are disclosed.[10] Furthermore, the NAPBC has included access to a credentialed genetic counselor to perform both pretest and posttest counseling as a standard component of each breast center's certification.[12]

Per NCCN and NAPBC guidelines, pretest counseling includes collection of a comprehensive family history; evaluation of the patient's cancer risk; generating a differential diagnosis and educating the patient on the penetrance of inheritance patterns; variable expressivity and the possibility of genetic heterogeneity; preparing the patient for possible outcomes of testing, including positive, negative, and uncertain findings; and obtaining informed consent. Posttest counseling centers discussion on the results of the genetic test and the recommended referrals for management options. In addition, the aim is to interpret the results in the context of personal and family history of cancer, providing opportunities to inform and test potential at-risk family members, and providing available resources such as online information or brochures for further reading, disease-specific support groups, and possible research studies (**Table 3**).[15]

Genetic counseling should also include a discussion of testing sensitivity and specificity, inconclusive genetic results, and variants of uncertain clinical significance. In addition, the NSGC has highlighted that attending to the psychosocial issues involved in genetic testing is a vital aspect of care that underpins health care behavior changes. Therefore, "genetic counseling is best offered in the context of a multidisciplinary team, which would include experts in genetic counseling, surgery, oncology, social work, nursing oncology, and psychology."[14]

GENETIC TESTING

The decision to proceed with genetic testing should be based on whether the test is clinically indicated and will affect clinical management of the patient, the results can be adequately interpreted, and (of paramount importance) patient preference. Given the complexity of communicating genetic concepts and information, it is only possible for patients to make an informed decision about testing once the pros and cons have been explained to them in an understandable way. Among patients presenting in the

Table 3
Lifetime cancer risk of common hereditary cancer syndromes

Column 1	General Population Risk (%)	*BRCA1* (%)	*BRCA2* (%)	TP53 (%)	PTEN (%)	PALB2 (%)	CDH1 (%)	ATM (%)	CHEK2 (%)
Breast	10–12	87	84	44–95	85	33–58	39–52	15–52	28–48
Ovarian	1.1	63	27	—	—	—	—	—	—
Melanoma	2–3.5	—	Increased	—	6	—	—	—	—
Endometrial	2.3–2.6	—	—	—	19–28	—	—	—	—
Colorectal	3–5	—	—	3–19	9–16	—	—	—	Increased
Thyroid	0.6–1.8	—	—	—	21–35	—	—	—	—
Bone Sarcoma	0.1	—	—	3–14	—	—	—	—	—
Soft Tissue Sarcoma	0.3	—	—	10–31	—	—	—	—	—
Brain	0.5	—	—	10–30	—	—	—	—	—
Gastric	0.6	—	—	—	—	—	Increased	—	—
Pancreatic	1.0	—	7	2–19	—	Increased	—	Increased	—
Prostate	12.8	16	20	—	—	—	—	—	—
Renal	1.2–2.1	—	—	—	15–34	—	—	—	—
Adrenocortical	—	—	—	Increased	—	—	—	—	—

context of a new breast cancer diagnosis, there is urgency in offering them genetic counseling and testing as appropriate, given that this information may inform medical or surgical management.[16]

In the context of a known family mutation, a negative test result in a family member unaffected with cancer is highly reassuring and considered informative in most cases. In contrast, when the first person in the family to be tested is an individual unaffected with cancer, there remain limitations in the interpretation of a negative result because it is not possible to distinguish between a true-negative and an uninformative result. A true-negative is someone not at risk for an inherited cancer (ie, a pathogenic variant has been previously identified in the family and accounts for the cancer phenotype observed in the family, and the individual tested does not have this previously identified mutation). An uninformative result means that an informative (or best testable) individual in the family was tested and not identified to have any pathogenic variant that explains the personal and family cancer history (suggesting that the pathogenic variant leading to cancer in this high-risk family may not have been discovered yet) or there is no living affected (best testable) family member available to test and confirm the existence of a pathogenic variant. Consequently, when suspicion of a hereditary syndrome is high, a negative result is not reassuring and should be interpreted as uninformative and management should be guided by family history. It is important to identify these patients upfront when initial testing is ordered, to set their expectations that, even if their tests do not identify a pathogenic variant, they will remain at high risk based on personal and/or family history. In these circumstances, it is also important to encourage testing among affected family members, if available, because this has the potential to clarify this type of uninformative result.

In circumstances in which multiple family members are affected, recommendations are first to test the family member with the youngest age at diagnosis, and those with bilateral disease, multiple primary cancers, or other cancers associated with the syndrome or most closely related to the patient.[11] In cases in which there is no living relative with the cancer in question, consideration may be given to testing first-degree or second-degree family members with other cancers thought to be related to the genetic mutation under suspicion. Although there are significant limitations in testing unaffected family members, it should be considered when no affected family member is available.

Genetic testing approaches may be grouped into targeted testing for mutations associated with a specific hereditary risk syndrome or more broadly approached with multigene panel testing through NGS-based technology that simultaneously analyzes a set of genes that are associated with multiple phenotypes.[17,18] When considering genetic testing options, it is important to consider the presenting phenotype, including the patient's personal and family cancer history, and physical examination. In this context, it is appropriate to test for specific genes based on a phenotype-directed approach or, alternatively, test through a multigene panel test while ensuring that the genes based on the patient's presenting phenotype are included. In cases of high suspicion that lack distinguishing features of a single inherited cancer syndrome, multigene panel testing provides a more expansive approach to hereditary syndrome identification and may be the best option. However, when testing through a multigene panel approach, it remains important to explain to the patient that some of the genes included on the panel have uncertain or even unproven associations with cancer risks and/or that there is a lack of evidence-based guidelines; furthermore, it is important to discuss the range of cancer risks of genes included on these tests, including those with moderate versus high penetrance, which carry substantial differences in management guidelines. In addition, it is important to discuss the high likelihood of identifying

a VUS result with testing for more genes, and that this type of result does not inform medical management.

Furthermore, there may be a role for multigene panel testing in individuals who have tested negative (indeterminate) for a single syndrome but whose personal or family history remains suggestive of an inherited susceptibility. Because commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important. Multigene testing can include intermediate-penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of these mutations.[10] As stated earlier, it is particularly important to recognize that not all genes included on available multigene tests are necessarily clinically actionable, leaving surgeons with a conundrum of surveillance and management decisions. In these circumstances, it remains critical to evaluate the evidence when providing management recommendations, given that there are harms to both overtreatment and undertreatment. Furthermore, there have been attempts by commercial laboratories to provide decision support to facilitate delivery of care to these patients, which can also result in misinformation. For example, several laboratories currently indicate that the lifetime risk for breast cancer among women with a germline mutation in the *ATM* gene is up to 60%, which is a level of risk at which risk-reducing mastectomy would be a consideration. However, this risk level is misleading given that it is a single allele (the 7279 C>G pathogenic variant) that has been established to confer this level of risk, and individuals with other pathogenic variants in the *ATM* gene have ~30% lifetime risk of breast cancer.[19] This type of information on test reports has high potential to be misinterpreted and lead to universal recommendations for bilateral mastectomy without the patients being given correct information about their cancer risks based on the specific *ATM* mutations with which they were identified.

As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely caused by that gene alone but may be influenced by gene/gene or gene/environment interactions. In addition, certain mutations in a gene may pose higher or lower risk than other mutations in that same gene. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives. In many cases, the information from testing for moderate penetrance genes does not change risk management compared with that based on family history alone. Mutations in many breast cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions.[20] Thus when these are identified, it is important to review the phenotype of the autosomal recessive condition and the carrier frequency, and advise the patient about carrier testing options, particularly among family members in their childbearing years. There is an increased likelihood of finding VUS when testing for mutations in multiple genes. It is for these and other reasons that multigene panel testing is ideally offered in the context of pretest and posttest counseling by individuals with professional genetics expertise.

In addition, genetic testing is often complicated by results that reveal a VUS, which occurs in roughly 10% to 13% of white patients who undergo *BRCA* gene sequencing.[21] Women of African descent have been noted to have higher rates of VUS, although populations that are genetically distinct or undertested may not show the VUS seen in the reference white/European population.[22] A VUS result is typically a missense mutation that is not involved in messenger RNA processing. For these results, it is important to determine the number of times the particular variant has been detected, whether it has been reported with another deleterious *BRCA* gene mutation, whether it is tracking with the cancer in the family, conservation of the change across

species, the region of the gene in which the change is located, change in the base pair that does not change the amino acid, or whether additional data based on functional studies are available.[23] Genetic variants that do not track with cancer, are seen with a proven deleterious mutation, are not conserved across species, are located in a region of the gene not known to have important functional significance, and have been evaluated through functional studies that suggest the change does not affect function are less likely to be of clinical significance to the patient. Understanding these concepts (or referring their patients to credentialed or certified genetics professionals) is paramount to surgeons because a recent study showed that 24% to 50% (high-volume vs low-volume cancer practices) of surgeons managed a VUS as they would a pathogenic mutation of *BRCA1/BRCA2*.[10] As the majority stakeholders in referral or ordering of genetic testing for patients with newly diagnosed breast cancer, surgeons must keep abreast of the current increase in genetic information. They must order testing for the right patients with the correct genes in a timely fashion, and accurately interpret results of genetic testing to appropriately guide treatment decisions such as risk-reducing mastectomy.

HIGHLY PENETRANT GENETIC SYNDROMES

BRCA1/BRCA2

It has now been roughly 20 years since the discovery of the *BRCA* genes, *BRCA1* and *BRCA2*, both of which encode for proteins involved in tumor suppression.[24] This breakthrough allowed the identification of patients with hereditary breast and ovarian cancer syndrome. *BRCA1* and *BRCA2* mutations comprise almost all hereditary breast cancers and these individuals are at a significantly increased risk of breast and ovarian cancer.[6,25,26] Initial epidemiologic studies suggested a lifetime risk for *BRCA1* carriers as high as 87% and *BRCA2* as high as 84%.[27,28] However, given that the sample population contained patients with a significant number of cancer diagnoses, bias likely existed favoring highly penetrant gene variants that resulted in an overestimation of the lifetime risk.[29] Subsequent meta-analysis has suggested that the risk of breast cancer from *BRCA1* ranges from 57% to 65%, and the risk from *BRCA2* from 45% to 49%.[29] Regarding ovarian cancer, the risk for *BRCA1* is 40% and these tumors are typically epithelial in origin, high grade, and advanced stage at diagnosis. The risk of ovarian cancer for *BRCA2* is 18%. For hereditary families with both breast and ovarian cancers, more than 90% are likely caused by mutations in the *BRCA1/BRCA2* genes.[6] Additional risks among *BRCA* mutation carriers include male breast cancer, prostate cancer, and pancreatic cancer, with *BRCA2* conferring higher risks for these cancers than *BRCA1*.

Pitfalls to risk identification of *BRCA* carriers include small biological family size, which may decrease sensitivity. In addition, in the rare cases of prophylactic operations that remove the susceptible organs or death before onset, the true incidence of the cancer remains unknown and this can hamper *BRCA* risk identification.[30]

BRCA1 and *BRCA2* are autosomal dominant genes; they may be inherited from either parent, resulting in the need for a complete 3-generation (maternal and paternal) family history. *BRCA1* and *BRCA2* mutations are rare in most populations, although much more common in certain populations. In the Ashkenazi Jewish population, 1 in 40 individuals carries 1 of 3 main disease-causing mutations, compared with an estimated prevalence of 1 in 300 for *BRCA1* and 1 in 800 for *BRCA2* in general populations.[31]

There has been a great deal of research into the tumor biology associated with *BRCA1/BRCA2* mutation carriers. Although *BRCA2*-associated breast cancers are

clinically comparable with sporadic cancers (estrogen receptor positive), *BRCA1*-related breast cancers are often more aggressive, show higher histologic grade, and are triple negative (estrogen receptor negative, progesterone receptor negative, and HER2 negative), with reports of *BRCA1* mutation ranging from 8.5% to 28% in patients with triple-negative breast cancer.[11,32–34]

Unlike other hereditary cancer syndromes, models exist to estimate the likelihood of identifying a mutation in the *BRCA1* or *BRCA2* genes. For example, the BRCAPRO statistical model and associated software estimate the likelihood of a germline mutation of *BRCA1* or *BRCA2* using family history and Bayes theorem.[35] As well as the predictive benefits, the limitations of the models and interpretation in the appropriate context should be noted. Penetrance of *BRCA1* and *BRCA2* have been variable and there may be additional genetic or environmental factors that play a role.

BRCA mutation–positive patients should undergo specific risk management strategies to optimize outcomes. Specifically, breast cancer screening guidelines have been proposed by the NCCN and are updated biannually.[10] Current recommendations include, but are not limited to, a discussion of risk-reducing mastectomies with women who are *BRCA* carriers. Patients should be counseled that there is a 90% to 95% reduction in breast cancer risk following prophylactic mastectomy.[35–39] In addition, reconstructive options should be proposed and plastic surgery consultation provided. Limited data exist regarding chemoprevention for *BRCA* carriers; however, because the mean cumulative lifetime risks for contralateral breast cancer have been estimated at 83% for *BRCA1* carriers and 62% for *BRCA2* carriers, efforts have been made to use chemoprevention as a strategy.[40] The Hereditary Breast Cancer Clinical Study Group reported that tamoxifen showed a statistically significant protective effect, with an odds ratio (OR) of 0.38 (95% confidence interval [CI], 0.19–0.74) against contralateral breast cancer among *BRCA1* mutation carriers, although no statistically significant difference was seen for patients with *BRCA2* (OR, 0.63; 95% CI, 0.20–1.50).[41] Some reports have shown the benefit of risk-reducing salpingo-oophorectomy, with a significant reduction in ovarian cancer for women who underwent prophylactic surgery compared with those who underwent close surveillance.[42,43] Oral contraceptives with estrogen and progestin have shown mixed results, with a protective effect against ovarian cancer in some studies but not in others.[44–46]

In addition to prevention strategies, another consideration is treatment of *BRCA* mutation–positive patients with breast cancer and involves usage of targeted agents such as poly (ADP-ribose) polymerase (PARP) inhibitors and platinum-based therapies.[47,48] PARP inhibitors are currently US Food and Drug Administration approved for *BRCA*-related ovarian cancer and are currently in clinical trials for breast cancer.

TP53/Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a very rare cancer syndrome thought to be responsible for approximately 1% of breast cancers.[49] The syndrome is associated with germline mutations in the *TP53* gene. LFS encompasses a breadth of cancer types and is viewed as a hereditary predisposition to cancer in general occurring at any point in an individual's lifetime. The cumulative lifetime cancer incidence nears 100%.[50] Mutations in the *TP53* gene, a tumor suppressor gene, comprise most LFS cases.[51–53] The more common LFS tumors, referred to as component tumors, include osteosarcomas, chondrosarcomas, soft tissue sarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinomas, with typical onset of a cancer in childhood.[53] The component tumors are thought to account for 63% to 77% of cancer diagnoses in individuals with LFS.[54–58]

Regarding breast cancer, it is the most common tumor in *p53* mutation carriers, as well as the most common second cancer diagnosis. Recent epidemiologic studies have suggested that although soft tissue tumors are most common among the very young and older patients with LFS, breast cancer was the most common diagnosis among those aged 18 to 44 years.[56] On histology, breast cancers are most commonly invasive ductal carcinomas.[55]

LFS was first identified in 1988 through examining 24 kindreds.[55] Subsequent efforts to broaden criteria to identify families with *p53* mutations were reported by Birch and colleagues[58] in 1994, who identified LFS-like (LFL) families. Nevertheless, a noted drawback is that both classic and LFL criteria rely on family history and do not capture patients with potential de novo germline *p53* mutations, which have been estimated to be from 7% to 20%.[54]

In 2001, Chompret and colleagues[57] developed criteria for identifying patients likely to carry *p53* mutations and included criteria that address families who display a collection of component tumors but also address individuals whose personal histories are suggestive of *p53* mutation even in the absence of a suggestive family history. The Chompret criteria were designed to include individuals who may potentially carry de novo *p53* mutations. Estimates place mutations in *p53* at 50% to 70% for the classic definition, 21% to 40% for the LFL definition, and 20% for Chompret.[55,58–64]

Studies that have examined overall cancer risk in *p53* mutation carriers show that the risk of developing cancer by 15 to 20 years of age is 12% to 42%, by age 40 to 45 years is 52% to 66%, by age 50 years is 80%, and by age 85 years is 85%.[57,63–66] When stratified by sex, female *p53* mutation carriers have a higher lifetime cancer risk compared with male carriers.[57,63,66] Individuals with LFS are also more likely to develop multiple primary tumors.[67]

Patients at risk for breast cancer should undergo a detailed discussion of risk management strategies and surveillance (**Table 4**).[11] Of note, recent articles have suggested that enhanced screening protocols may detect early-stage disease and potentially lead to improved outcomes in patients with LFS, commonly referred to as the Toronto protocol.[68–70] The surveillance protocol included physical examinations, laboratory studies, and imaging with ultrasonography, brain MRI, and rapid total-body MRI scans to minimize radiation exposure. A prospective, observational study of 8 families with LFS who were followed either with enhanced surveillance (n = 18) or routine institutional follow-up care (n = 16; 1 patient with LFS was in both groups) showed a significant difference in overall survival at 3 years, with 100% survival in the surveillance group, and 21% in the group without enhanced surveillance.[70]

Although there are no data for patients with LFS regarding risk reduction surgery, NCCN guidelines recommend discussion on a case-by-case basis.[10] However, breast cancer remains the first and second most common cancer affecting patients with *TP53* and, thus consideration for risk-reducing surgery is reasonable. For family members of patients with LFS, breast cancer screening should begin between age 20 and 25 years or, if younger than 20 years, at the age of the earliest known breast cancer in the family. Breast screening recommendations in LFS mirror those for *BRCA*-related breast and ovarian cancer syndrome management and vary with patient age. For women aged 20 to 29 years, annual breast MRI screening with contrast is preferred, or mammogram if MRI is not available. For women aged 30 to 75 years, annual mammogram and breast MRI screening with contrast is recommended. An individualized approach is recommended for women more than 75 years old. Screening for other component cancers should be performed in the setting of a multidisciplinary genetics clinical service.

Table 4
Screening recommendations and management strategies

	Recommend Breast MRI	Age to Begin (y)	Recommend Prophylactic BSO	Age (y)	Recommend Prophylactic Mastectomy	Other Recommendations
Intervention Based on Pathogenic Variant Alone	BRCA1 BRCA2 TP53 PTEN PALB2 CDH1 CHEK2 ATM	25 25 20 30 30 30 40 40	BRCA1 BRCA2	35–45 or when identified at later age	BRCA1 BRCA2 TP53 PTEN CDH1	1. BRCA2: annual skin examination, pancreatic screen if fam history 2. TP53: annual rapid total-body MRI, skin examination, neurologic examination, CBC, UA; colonoscopy q 2–5 y starting age 25 y 3. PTEN: annual thyroid and transvaginal US and skin examination starting age 30 y, colonoscopy and renal US q 2y starting age 40 y 4. CDH1: EGD 5. CHEK2: colonoscopy q 5 y
Insufficient Data for Intervention Based on Pathogenic Variant Alone	—	—	PALB2	—	ATM CHEK2 PALB2	ATM: can consider mastectomy based on addition of family history

Abbreviations: BSO, bilateral salpingo-oophorectomy; CBC, complete blood count; EGD, esophagogastroduodenoscopy; q, every; UA, urinalysis; US, ultrasonography.

In the context of a breast cancer diagnosis, detection of a *TP53* mutation may refine surgical treatment, with some patients choosing to undergo bilateral mastectomy to reduce risks of a second primary breast cancer. Furthermore, studies have suggested that radiation treatment as part of a primary cancer treatment may increase the risks of subsequent cancers among individuals with germline *TP53* mutations.[71,72] The NCCN practice guidelines state that "Therapeutic radiation treatment for cancer should be avoided when possible"[10] among patients with LFS. A recent French study of more than 400 patients with LFS reported a high rate (43%) of multiple primary cancers, most of which were cancers that developed following an initial cancer diagnosis.[72] Treatment records were available on a subset of patients who received radiation treatment of their first tumor, which showed that 30% developed secondary tumors in the radiation field, within 2 to 26 years (mean, 10.7 years) following their initial cancer treatment.[72] Therefore, caution is advised before offering surgical choices that are contingent on subsequent radiation administration for completion of standard of care.

PTEN/Cowden Syndrome

The *PTEN* hamartoma tumor syndrome (PHTS) is a rare hereditary cancer syndrome arising from germline mutations in *PTEN* (phosphate and tensin homolog), a tumor suppressor gene. These mutations manifest in a spectrum of clinical disorders characterized by overgrowth in different organ systems. PHTS encompasses Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, adult Lhermitte-Duclos disease, Proteus and Proteus-like syndrome, and autism spectrum disorders with macrocephaly.[73–77]

The best studied of these is CS, an autosomal dominant disorder with an incidence of approximately 1 in 200,000, although, given the difficulty of diagnosis, it may be underestimated.[78,79] The initial estimated penetrance of *PTEN* mutation was roughly 80%, although expanded criteria have decreased that figure to approximately 25%.[79–81] Although *PTEN* mutations are the most common, mutations in other genes, such as *SDHx* and *KILLIN*, have been reported in small cohorts of patients.[81,82]

The lifetime risk for breast cancer for women diagnosed with CS has been estimated at 25% to 50%, with an average age of 38 to 50 years at diagnosis.[83] The lifetime breast cancer risk for *PTEN* hamartoma syndrome ranged from 67% to 85% in 3 studies, with increased risk beginning around the age of 30 years.[84–86] Additional studies have shown that women with PTEN mutations and a breast cancer diagnosis have a 29% risk of a secondary breast cancer within 10 years.[87]

Patients with suspicion of CS/PHTS should be assessed with a detailed history that should explore both benign and malignant conditions associated with the syndrome and a physical examination with attention to skin and oral mucosa for hamartomas, breast, and thyroid gland.[10] The classic feature of CS is development of multiple hamartomas of the skin and mucosa. A thorough physical examination, including head circumference measurement and examination for skin manifestations, is an important component of assessing for CS. However, a lack of hamartomas does not exclude CS.

In 1995 the International Cowden Consortium produced the first diagnostic criteria for CS.[79] Since that time, criteria have evolved and been modified. Of note, the criteria are used to assess the need for further risk assessment and genetic testing but are not intended to serve as clinical diagnostic criteria. Given the complexity and degree of variability in CS, making a formal diagnosis is difficult except in the most obvious of cases. In cases of high suspicion, a negative genetic test result may be uninformative

for the patient and her family. In contrast, a positive result or VUS in an individual without classic features of CS can lead to uncertainty regarding how aggressive to be about screening and prevention measures.

The highest risk of cancer associated with CS is for female breast cancer, with estimates of cancer risk ranging from 25% to 85%. Other cancers comprising CS include thyroid cancer, with a risk of 3% to 38%, and endometrial cancer, with a risk of 5% to 28%. In addition, renal cell cancer with a risk estimate of 34%, melanoma with a risk of 6%, and colorectal cancer with a risk of 9% have also been reported.[74,84]

As such, patients with PTEN (CS) should undergo specific risk management strategies to optimize outcomes (see **Table 4**). Recommendations are for annual breast MRI starting at age 30 years followed by consideration of risk-reducing surgery.[10] In addition, annual thyroid ultrasonography, transvaginal ultrasonography, and a skin survey should likewise begin at age 30 years. Colonoscopy and renal ultrasonography scans begin at age 40 years and should be performed every 2 years.

Other High-Penetrance Genes

PALB2

PALB2 (partner and localizer of *BRCA2*) is a Fanconi anemia gene that was initially identified as a protein involved in *BRCA2* genome caretaker functions and subsequently showed interaction with *BRCA1*.[87,88] Fanconi anemia arises when germline loss-of-function mutations are biallelic, although monoallelic mutations are associated with breast and pancreatic cancer.[89] Studies have shown that 1% to 3% of women with breast cancer possess a *PALB2* mutation.[90,91]

The lifetime breast cancer risk in women with a *PALB2* mutation is 14% by age 50 years and 35% by age 70 years; however, the risk also increases with increasing number of relatives affected with breast cancer.[89] Breast cancer risk by age 70 years for those with no first-degree relatives with breast cancer was 33%, compared with 58% in those with 2 first-degree relatives.[89] Contralateral breast cancer was reported in 10% of *PALB2* carriers and the 10-year survival among *PALB2* carriers with breast cancer was 48%, compared with 72% in *BRCA1* mutation carriers and 75% in noncarriers.[91] Thus, there are suggestions that *PALB2* mutations may be associated with aggressive breast cancer.

NCCN recommendations include annual mammogram for *PALB2* mutation carriers beginning at age 30 years and that additional consideration should be given to breast MRI screening (see **Table 4**).[10,20] The NCCN also recommends consideration of risk-reducing mastectomy. However, because of an uncertain association between *PALB2* and increased ovarian cancer risk, there is no recommendation to consider salpingo-oophorectomy as a risk reduction strategy at this time.[92,93]

CDH1

In 1998, linkage analysis suggested that germline mutations in *CDH1*, which encodes the tumor suppressor protein E-cadherin, were associated with hereditary diffuse gastric cancer.[94] A year later, *CDH1* mutations were also shown to be associated with lobular breast cancer.[95] Studies have shown the lifetime risk for breast cancer to be 39% to 52%.[96–98] Pertaining to lobular breast cancer, updated clinical guidelines state that established criteria for *CDH1* genetic testing include a personal or family history of diffuse gastric cancer and lobular breast cancer with 1 diagnosed before 50 years of age. Consideration of genetic testing should be given with a history of bilateral lobular breast cancer or family history of 2 or more cases of lobular breast cancer before age 50 years.[99] The NCCN recommends annual mammogram, or consideration of a breast MRI, starting at age 30 years and considering earlier screening in patients

with a family history of early-onset breast cancer (see **Table 4**).[10] In addition, risk-reducing mastectomy should be discussed with patients with *CDH1*.

MODERATE PENETRANCE GENES

ATM

Biallelic germline mutations of the ataxia telangiectasia (*ATM*) gene cause ataxia telangiectasia, a pediatric neurologic disorder associated with telangiectasias; immunodeficiency; sensitivity to ionizing radiation; and a 20% to 30% lifetime risk of lymph, gastric, breast, nervous, skin, and other cancers.[99,100]

The association between *ATM* genetic variants and breast cancer risk is not fully clarified. Studies have reported a risk of breast cancer ranging from 15% to 52%.[19,101–104] A recent meta-analysis showed that the lifetime risk of breast cancer for *ATM* mutation carriers was 38% compared with carriers of the c.7271T>G missense mutation, who have a 69% risk of breast cancer by age 70 years.[19]

The NCCN recommends annual screening mammogram for women with an *ATM* gene mutation beginning at age 40 years and consideration of annual breast MRI (see **Table 4**). In addition, mastectomy may be considered based on family history.[10] Although there has been concern that radiation exposure in heterozygous carriers may increase breast cancer risk, there is insufficient evidence of an association at this time. A meta-analysis reported that radiation therapy is not contraindicated in patients with a heterozygous *ATM* mutation.[19] Thus, per current NCCN guidelines, *ATM* heterozygosity (ie, an individual with a single pathogenic variant in the *ATM* gene) is not a contraindication to receipt of radiation therapy in the context of a breast cancer diagnosis.

Breast cancer has long been linked with the *ATM* gene, which is fairly well known and characterized given that biallelic mutations are causative of ataxia telangiectasia, a childhood-onset progressive neurologic disorder associated with telangiectasias, immunodeficiency, sensitivity to ionizing radiation, and increased risks for malignancies (primarily leukemias and lymphomas). Approximately 1% to 3% of the general population may be heterozygous carriers of an *ATM* mutation.[186,187] Studies on the association of *ATM* heterozygous mutations on breast cancer risk have conflicting results, although the 2 largest provide the most convincing evidence of an association.[188,189] The risk is estimated at 15% to 52%, and the relative increase in risk may be even higher for women younger than 50 years.[188–192] *ATM* mutations have been found to cosegregate in several families with multiple cases of pancreatic cancer. Stomach, ovarian, bladder, and colon cancer risks may also be increased, although the evidence of a strong association is less compelling.[189,192] Although breast cancer risk is modest, it has been proposed that *ATM* carriers may need different approaches to treatment o.

CHEK2

CHEK2 (cell cycle checkpoint kinase 2) genes are involved in protein signaling related to DNA double-strand breaks. In a study of patients with breast cancer and a strong family history of breast or ovarian cancer but without *BRCA*, a *CHEK2* mutation was detected in 5%.[105] This mutation is more frequent in northern and eastern European populations.[106] The lifetime risk for breast cancer in women with a *CHEK2* mutation ranges from 28% to 37% and is higher in women with stronger family histories of breast cancer than in those without.[107,108] The specific *CHEK2* variant, 110delC, has been shown to increase breast cancer risk by more than 2-fold when stratified by age and sex.[109] Another study showed that heterozygous 1100delC carriers

have a higher risk of developing ER-positive breast cancer, and therefore may be considered for chemoprevention with tamoxifen.[110,111]

The NCCN recommends annual mammogram starting at age 40 years for women with a *CHEK2* mutation and consideration of annual breast MRI (see **Table 4**).[10] For *CHEK2*, no data exist regarding the benefit of risk-reducing mastectomy for women, although, given the context of family history, it may be considered. As for colorectal cancer, recommendations are for colonoscopy every 5 years, and are adjusted based on colonoscopy findings and family history.

NEWER GENES WITHOUT A PROVEN ASSOCIATION WITH BREAST CANCER

The *RAD51* family of genes is involved in DNA damage repair via the homologous recombination pathway. Although *RAD51C* and *RAD51D* have been shown to be associated with increased risk for ovarian cancer, there is currently insufficient evidence that they are associated with increased breast cancer risk.[11] Patients with *RAD51C* and *RAD51D* mutations should be managed as average-risk patients.[11] However, they are at an increased risk for ovarian cancer and consideration for risk-reducing bilateral salpingo-oophorectomy is reasonable.[112,113]

SUMMARY

With nascent advances in genomic technologies, genetic counseling and testing for inherited cancer predisposition is rapidly evolving. The dissemination of next-generation multigene sequencing panels will continue to provide an opportunity for the identification of genetic aberrations for patients at high risk for cancer. However, the identification of those patients involves surgeon awareness and a thorough clinical evaluation, including a systemic history and physical examination. In concert with a rigorous 3-generation family history, high-risk patients can be identified and decisions based on currently available evidence can then be made regarding further counseling and use of genetic testing to identify hereditary breast cancer syndromes. As research unveils additional cancer susceptibility genes, further work regarding the interpretation and implementation of clinical management plans will be needed. Surgeons, therefore, must keep abreast of these advances and, at the minimum, refer patients to genetic services for in-depth evaluation for risk assessment, testing, and results interpretation. For most surgeons, having a well-established multidisciplinary team comprising genetic counselors, oncologists, psychosocial experts, other specialists (plastic surgeons, dermatology, gastroenterology, gynecology), and imagers vested in inherited cancer syndromes is imperative. The advances in genomic testing bring forth an exciting time, with surgeons at the front lines of identification and management of many of these high-risk individuals. However, the tremendous potential for genomic testing to prevent disease and positively affect health can only be realized if patient testing and follow-up care are guided by evidence-based recommendations, and accessible across all segments of the population.

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