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PRACTICE RESOURCE

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Risk assessment and genetic counseling for hereditary breast and ovarian cancer syndromes—Practice resource of the National Society of Genetic Counselors

Janice L. Berliner[1] | Shelly A. Cummings[2] | Brittany Boldt Burnett[3] | Charité N. Ricker[4]

[1]Genetic Counseling Department, Bay Path University, East Longmeadow, MA, USA

[2]Myriad Genetics, Inc, Salt Lake City, UT, USA

[3]Sharp HealthCare, San Diego, CA, USA

[4]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Correspondence
Janice L. Berliner, Genetic Counseling Department, School of Education, Human and Health Sciences, Bay Path University, East Longmeadow, MA, USA.
Email: jberliner@baypath.edu

Abstract

Cancer risk assessment and genetic counseling for hereditary breast and ovarian cancer (HBOC) are a communication process to inform and prepare patients for genetic test results and the related medical management. An increasing number of healthcare providers are active in the delivery of cancer risk assessment and testing, which can have enormous benefits for enhanced patient care. However, genetics professionals remain key in the multidisciplinary care of at-risk patients and their families, given their training in facilitating patients' understanding of the role of genetics in cancer development, the potential psychological, social, and medical implications associated with cancer risk assessment and genetic testing. A collaborative partnership of non-genetics and genetics experts is the ideal approach to address the growing number of patients at risk for hereditary breast and ovarian cancer. The goal of this practice resource is to provide allied health professionals an understanding of the key components of risk assessment for HBOC as well as the use of risk models and published guidelines for medical management. We also highlight what patient types are appropriate for genetic testing, what are the most appropriate test(s) to consider, and when to refer individuals to a genetics professional. This practice resource is intended to serve as a resource for allied health professionals in determining their approach to delivering comprehensive care for families and individuals facing HBOC. The cancer risk and prevalence figures in this document are based on cisgender women and men; the risks for transgender or non-binary individuals have not been studied and therefore remain poorly understood.

KEYWORDS

cancer risk assessment, cascade testing, family history, genetic counseling, genetic testing

1 | INTRODUCTION

Genetic counseling and testing have been an important part of cancer care for many years. The identification of pathogenic and likely pathogenic variants (P/LPV) in high- and moderate-penetrance genes can impact treatment strategies, surveillance, and preventative surgeries. In 2013, the NSGC published a practice guideline regarding cancer risk assessment for hereditary breast and ovarian cancer related to P/LPV in the *BRCA1* and *BRCA2* genes (Berliner et al., 2013), a topic that had been studied extensively in the more than twenty-five years since those genes were identified. However, with the expanded genetic testing that is now available for other genes related to hereditary breast and/or ovarian cancer, a growing body of literature has emerged on risk assessment, medical

management, psychosocial issues, and genetic testing for individuals from moderate or high-risk breast and/or ovarian cancer families. Much less is known about the appropriate clinical management for individuals with P/LPV within less common, high-penetrance cancer-susceptibility genes or moderate-penetrance genes. This is an area of ongoing research that will continue to inform genetic counseling and testing. The provision of patient resources is important, and therefore, it is crucial that the most updated information be available to practitioners.

Please note, while older literature refers to 'mutations', the American College of Medical Genetics guidelines recommend the use of the term variant, with appropriate descriptors including benign, likely benign, variant of uncertain significance, likely pathogenic and pathogenic (Richards et al., 2015). These terms will be used throughout this practice resource.

1.1 | Purpose

To provide a resource for allied health professionals in (a) understanding the use of established breast cancer risk estimation models; (b) determining appropriate individuals for genetic testing, as well as the most appropriate test(s) to perform; (c) knowing when to refer individuals for formal genetic counseling; and (d) understanding published guidelines for the medical management of individuals at elevated breast and ovarian cancer risk.

1.2 | Background

Most cancer susceptibility likely arises from a combination of DNA sequence variants, each of which, by itself, only modestly increases risk. High-penetrance gene P/LPVs, however, often lead to significant changes in the functions of the associated protein products and are associated with higher risks for cancer development than in the general population. Testing high-penetrance genes in selected individuals has clinical utility, such as informing medical decision-making and helping to prevent or decrease adverse health outcomes (Robson & Offit, 2007). An estimated 10% of breast cancer occurs in the setting of hereditary, single-gene P/LPVs such as those within *BRCA1* and *BRCA2* (Claus et al., 1996; Foulkes, 2008). Various studies have shown that multigene panels, which test high- and moderate-risk breast cancer genes beyond *BRCA1* and *BRCA2*, increase the yield of P/LPVs, though the size of that increase is dependent on the cohort tested, as well as the size and composition of the panel utilized (Beitsch et al., 2019; Bonache et al., 2018; Hauke et al., 2018; Kurian et al., 2014; Ricker et al., 2016; Rosenthal et al., 2017; Zheng et al., 2018). In unselected populations, approximately 0.5% of those undergoing exome sequencing have been found to be *BRCA1/2* carriers (Abul-Husn et al., 2019; Grzymski et al., 2020; Manickam et al., 2018). About 18% of all ovarian cancers have been associated with *BRCA1* or *BRCA2* P/LPVs, while another 6% have been attributed to variants in other genes, discussed below (Walsh et al., 2011). While breast cancers represent less than 1% of the total cancer diagnoses among men, 4%–40% of men who have breast cancer have been found to have P/LPVs within *BRCA1* or *BRCA2* (Thorlacius et al., 1997; Friedman et al, 1997). Other variants, such as the c.1100delC PV in *CHEK2*, also contribute to male breast cancer risk (Hallamies et al., 2017).

BRCA1 and *BRCA2* (collectively referred to as *BRCA*) are tumor suppressor genes. Their protein products are involved in the cellular response to DNA damage and double-stranded DNA repair. Breast cancers associated with *BRCA1* P/LPVs are far more likely than their sporadic counterparts to be triple-negative (negative for estrogen and progesterone receptors as well as Her2/neu overexpression) (Atchley et al., 2008). The cancer types associated with P/LPVs in *BRCA1* and *BRCA2* originally were thought to be only of the breast, ovary, and fallopian tubes (Finch et al., 2006; Medeiros et al., 2006). However, the cancer spectrum includes male breast (Evans et al., 2010), prostate (Edwards et al., 2010; Giri et al., 2017; Pritchard et al., 2016), pancreatic (Carnevale & Ashworth, 2015; Peterson and Hruban 2003; van Asperen et al., 2005; Mersch et al., 2015), and melanoma (Hearle et al., 2003). Serous or serous-like endometrial cancer, colorectal cancer, and leukemia have been reported, but more data are needed to confirm a possible association (Iqbal et al., 2016; Saule et al., 2018; Shu et al., 2016).

In the general population, approximately 12% of women will develop breast cancer at some point in their lives, while approximately 1.3% will develop ovarian cancer (SEER data, 2014–2016). Although most of these cancers will not be attributable to *BRCA1* or *BRCA2*, identifying those who do carry P/LPVs is critical for patients and their potentially at-risk family members. The authors will poiniat out that cancer risk and prevalence figures in this document are based on cisgender women and men; and the risks for transgender or non-binary individuals are unknown at this time.

Meta-analysis estimates of the prevalence of *BRCA* P/LPVs have shown: 0.2 to 0.3% of the general population carry P/LP variations in these genes, including 3% of women with breast cancer, 6% of women with breast cancer onset prior to 40 years of age, 10% of women with ovarian cancer at any age, and 20% of high-risk families, as defined by Nelson et al., 2014. Among Ashkenazi Jewish women, prevalence is 2% in unselected cohorts and 10% in high-risk families (Nelson et al., 2014). *BRCA* P/LPVs have been identified in individuals of all racial and ethnic backgrounds where the genes have been studied. There is no single accepted definition of 'high risk', and this designation can be determined several ways depending on the cancer type. There may be one specific factor that puts a patient into this category, or a combination of factors working together can increase risk. We chose to use 'high-risk' as a common and acceptable term.

Lifetime cancer penetrance estimates are largely derived from clinically ascertained identified populations, enriched for individuals with strong family histories, rather than unselected patients in whom risk has been shown to be lower. This is suggestive of modification of risk by other factors, such as modifier genes (Antoniou et al., 2003). Additionally, the majority of the data used to generate cancer risk and prevalence estimates are based on clinical and

research cohorts of individuals of predominantly European, White ancestry; therefore, the subtleties of population-level effects may not be well appreciated. Of note, these are also studies of cisgender women and men; the risks for transgender or non-binary individuals have not been studied and therefore remain poorly understood.

Women with germline *BRCA1* P/LPVs are estimated to generally thought to face a 60%–72% risk of breast cancer to age 70, while those with *BRCA2* P/LP are estimated to have a 55%–88% risk. The ovarian cancer incidence by age 70 is 44%–59% in *BRCA1* P/LPV carriers and 17%–35% in *BRCA2* carriers (van der Kolk et al., 2010; Kuchenbaecker et al., 2017; Mavaddat et al., 2013). The 10-year risk for contralateral breast cancer is 17%–34% in women with *BRCA1* P/LPVs, and 7%–30% in those with *BRCA2* P/LPVs (Kuchenbaecker et al., 2017; Mavaddat et al., 2013; Menes et al., 2015; Metcalfe et al., 2011; Molina-Montes et al., 2014). These studies have shown that as age at diagnosis decreases, risk for a contralateral breast cancer increases (Kuchenbaecker et al., 2017; Menes et al., 2015; Metcalfe et al., 2011; Molina-Montes et al., 2014). It is critical to think beyond *BRCA1* and *BRCA2*, as breast and ovarian cancer can also be seen in other hereditary cancer syndromes, such as Cowden (associated with P/LPVs mostly in *PTEN*) (RR for breast cancer 2.0–5.0), Li–Fraumeni (*TP53* gene) (RR for breast cancer 4.3–9.3), Peutz–Jeghers (*STK11* gene) (RR for breast cancer 2.0–4.0), and hereditary diffuse gastric cancer (*CDH1* gene) (RR for breast cancer 5.9–7.3) (Tung et al., 2015). These syndromes are often characterized by a different constellation of cancers than those associated with *BRCA* P/LPVs.

Breast cancers can also be associated with P/LPVs in some moderate- and low-risk genes (Lindor & Greene, 2008; Siraj et al., 2017), such as *PALB2*, *CHEK2*, and *ATM*. On the basis of two large case–control analyses, Easton et al. (2015) calculated an estimated relative risk of breast cancer of 2.8 for *ATM* P/LPVs and 3.0 for *CHEK2* P/LPVs, including lower-risk missense variants (Han et al., 2013) and higher-risk truncating variants (Tung et al., 2016). While ovarian cancer is mainly associated with P/LPV in *BRCA1* and *BRCA2*, it may also be associated with variants in other 'breast cancer genes' such as *BARD1*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* (Norquist et al., 2015; Walsh et al., 2011). As the number of genes that can be tested continues to grow, the importance of providers staying attuned to emerging data and changing guidelines about P/LPV in these genes and the management implications is increasingly more important.

Men remain under-tested for hereditary breast and/or ovarian cancer syndromes (Childers et al., 2018). While some of the genes discussed above are not currently known to increase cancer risk in men, the risks associated with a P/LPV in *BRCA1* and *BRCA2* are known. In a study by Ibrahim et al. (2018), prostate cancer was the most common cancer seen in the 102 male *BRCA* carriers studied, followed by breast cancer. Most of these carrier men had P/LPVs in *BRCA2*. Additionally, men who carry P/LPVs in any of these genes are just as likely to pass these variants on to their children as their female counterparts.

Advances in sequencing technology have provided the ability to routinely test for more genes that may explain the personal and family history of breast and/or ovarian cancer, rather than the gene-by-gene approach that was previously utilized. While the choice of what type of testing to offer is largely the purview of the health care provider, multigene panel testing may be particularly useful when there is a significant family history suggestive of multiple syndromes or when previous, more limited, germline testing was uninformative and there is still concern for an inherited predisposition to cancer.

Multigene panel testing can result in a higher probability of finding a variant of uncertain significance (VUS) or a P/LPV in any of the genes suspected based on personal and/or family history (Idos et al., 2019; Yurgelun et al., 2015). It also increases the likelihood that a VUS or an unexpected P/LPV may be found in other genes included in the panel. All of these clinical situations can present challenges to providers and patients (Marcus, et al., 2015; Slavin et al., 2015). As such, it is important that providers be aware of how to navigate and manage these findings. Consultations with a medical professional who has expertise in cancer genetics are especially important with these findings, given their complexity and the potential difficulty in understanding how to interpret and navigate the information in families.

2 | PRETEST AND RISK ASSESSMENT CONSIDERATIONS

2.1 | Utilization of genetic evaluation resources

Although professional guidelines for genetic counseling referral vary among organizations, they are consistently based on the recognition of clinical features that increase the likelihood of hereditary susceptibility to breast and ovarian cancer (ACMG, 2015; ACOG Practice, 2009; ASCO 2003; Berliner et al., 2013; Berliner & Fay, 2007; NCCN v1. 2021; Riley et al., 2012; SGO, 2014). These criteria do not necessarily equate to guidelines for genetic testing. Broader referral criteria allow for a larger number of patients to benefit from risk assessment and identify appropriate candidates for genetic testing who would be missed using more stringent criteria. Despite differences in professional society guidelines about when to offer genetic testing, the majority follow the general algorithms outlined by the National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guideline (NCCN v1. 2021).

As the number of individuals who qualify for clinical genetic testing increases, there is a growing need for the provision of appropriate genetics education and evaluation by various types of professionals. The traditional clinical genetics model of certified geneticist/genetic counselor providing complete pre- and post-test evaluation and counseling cannot meet the need for cancer genetic testing. A growing body of clinical literature has emerged, focused on how to effectively engage genetics providers into alternative service delivery models, including group counseling, telemedicine, genetic counselors embedded in

oncology clinics, genetics education provided by other healthcare providers with referral to genetics post-testing, etc. (Fournier et al., 2018; McCuaig et al., 2018, 2019; Pierle & Mahon, 2019). A broad array of educational tools and programs for allied health care professionals may assist in meeting the triage needs for genetic testing, as these tests become more commonplace and demand continues to grow. Direct-to-consumer testing or consumer-driven options place a greater responsibility on professionals to interpret and communicate the limitations and utility of this information to consumers, rather than obviate the need for those professionals (Fournier et al., 2018; McCuaig, et al., 2018; Solomons et al., 2018).

2.2 | Evaluating a comprehensive family history can be a vital component of risk assessment and adherence to published guidelines

Individual and family risk assessment has become a more simplified process with widely available tools and resources. However, one needs to know what questions to ask and what information to collect. It is important to remember that cancer is a common condition and it is likely to be observed on both sides of the family. The healthcare provider must assess each side of the family separately and devise the most appropriate plan for testing based on level of risk. There are several clinical clues to look for when considering the presence of a hereditary susceptibility to cancer. These include, but are not limited to (Banks et al., 2013; Forman & Schwartz, 2019; Hampel et al., 2015):

- cancer occurring at an earlier than average age (e.g., premenopausal breast cancer)
- multicentric development of cancer in the same organ and/or bilateral development of cancer in paired organs
- development of more than one primary cancer, associated with cancer predisposition genes, in a single individual; important exceptions should be noted for common cancers with clear non-inherited etiologies, such as non-melanoma skin cancers, lung cancer, and cervical cancer
- clustering of cancers consistent with a specific syndrome (e.g., breast and ovarian)
- cancer of the same type in two or more relatives (on the same side of the family)
- excess number of cancers in the family
- particular ethnic groups known to be at higher risk of hereditary cancer (e.g., *BRCA1/2* P/LPVs in Ashkenazi Jewish populations)
- familial cancer diagnoses suggestive of an autosomal dominant pattern
- rare tumors with a strong association with specific cancer syndromes or a significant heritable component, such as male breast cancer, adrenocortical carcinoma, etc.

While the cornerstone of genetic counseling has been based on the segregation of cancer in the family, the advent of multigene panel testing has uncovered that there are single indications outside of having a strong family history of cancer that warrant consideration for genetic testing. Couch et al demonstrated that P/LPVs in predisposition genes were present in about 15% of patients with triple-negative breast cancer (TNBC) unselected for family history of cancer (Couch et al., 2015). Ovarian cancer, male breast cancer, pancreatic cancer, and metastatic prostate cancer diagnosed at any age, regardless of family history, have all been added recently to NCCN guidelines as single indications for testing, as has early-onset breast cancer (age 45 years or under) (NCCN v1. 2021). Population-level genomic screening, aimed at identifying individuals with P/LPVs in *BRCA1* and *BRCA2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* and genes associated with familial hypercholesterolemia, has found that the majority of individuals with these conditions were previously undiagnosed, suggesting that broader approaches may be needed to more comprehensively identify at-risk individuals in the population (Buchanan et al., 2020; Grzymski et al., 2020).

The genetic contribution to cancer risk is not limited to high and moderate-risk genes. Common single nucleotide polymorphisms (SNPs) associated with increased breast cancer risk, for example, have been identified by genome-wide association studies (Easton, Pooley, et al., 2007; Mavaddat et al., 2015; Michailidou et al., 2013, 2017). The magnitude of risk conferred by these SNPs is low when considered individually, typically only a relative risk of 1.05 to 1.3. However, when combined, these SNPs may explain a portion of the remaining heritability of breast cancer and be used to estimate breast cancer risk clinically for women who do not carry more highly penetrant gene variants (Dite et al., 2016; Mealiffe et al., 2010). Estimates of risk using SNP-based testing (polygenic-risk scores) in women who are not of European ancestry are not available at this time, but this area is currently being evaluated (Mavadatt et al, 2015). This disparity stems from the underrepresentation of non-European cohorts in genetic discovery efforts (Martin et al., 2019) and highlights the need for funding and focus on diversification of research cohorts. Further research is necessary to understand the integration of these polygenic scores into risk assessment and management in other cancers such as ovarian, colon, and prostate, as well as counseling and communication strategies to insure effective communication of polygenic information to patients and within families (Yanes et al., 2020).

Even though we are learning that the family history might not be the sole guiding force for the decision to proceed with genetic testing, it remains integral to the risk assessment process for several reasons. Evaluating and documenting all the cancers in the family aids our understanding of less well-known genes and even sheds light on the phenotype associated with genes thought to be well understood. Another important reason for taking a comprehensive family history also remains important, as there is evidence that the severity of the family history can impact the risk associated with certain probability that there is a P/LP cancer risk variant in the family. For example, the cancer risks associated with *CHEK2* appear to be dependent on the strength of the family history of breast cancer, with women who have a P/LP *CHEK2* variant in the context of a positive

family history of breast cancer (e.g., affected 1- and 2-degree relatives) having a higher breast cancer risk than those without a family history (Cybulski et al., 2011). Family history collection helps identify members who are at risk and may be eligible for testing if a P/LPV is present in the family (cascade testing). Lastly, family history is of particular relevance in the interpretation of negative test results, since individuals may still be at empiric risk for cancer based on their family histories. Despite advances in genetic testing, there are still heritable components to risk which remain unmeasured. This is a key component of post-test counseling that merits discussion with patients to insure appropriate risk assessment. A detailed review of the clinical features and genetic testing recommendations for all the genes associated with breast and ovarian cancer is outside the scope of this resource, but there are excellent resources available for this purpose (Lindor & Greene, 2008; NCCN v1. 2021).

2.3 | Published guidelines should be consulted for guidance on when to refer patients for genetic counseling, when consideration of genetic testing is appropriate, and appropriate medical management.

Significant advances have been made in clinically available molecular diagnostic testing for cancer predisposition genes, the counseling and testing process, and medical management options available for patients. Initially, genetic testing of the *BRCA1* and *BRCA2* genes was only offered to patients with high probability of carrying P/LPVs. In such families, genetic test results often confirm the underlying molecular etiology of cancer risk in the family and allow for at-risk relatives to be identified by testing for the known familial variant. However, given that patients with no or less striking family histories of cancer may also be appropriate candidates for genetic testing (Gonzalez-Angulo et al., 2011; NCCN v1. 2021), identification of a P/LPV may dramatically alter the course of medical management as well as treatment options for a patient whose prior probability of a P/LPV is low. Even in instances when a patient presents with a 'negative' direct-to-consumer test report, healthcare providers must continue using traditional criteria for referral for genetics evaluation, as there are limitations to these analyses. For those who are at high risk, given their personal and/or family history, population-based genetic tests may not be appropriate and might not replace targeted single-gene or panel testing coordinated by a genetics professional. As noted above, a broad array of educational tools and population-based empiric models for healthcare professionals, such as the Tyrer–Cuzick online software and others (see Table 1), may assist in meeting the triage needs for genetic testing. The American Society of Clinical Oncology (ASCO) guidelines suggest that the clinical judgment of a healthcare provider experienced in cancer genetics should be relied upon to determine the appropriateness of genetic testing, as opposed to using a numerical threshold (ASCO, 2003). This is consistent with the guidelines of other professional organizations, most of which provide criteria to assist in determining which patients should be offered further education and counseling, so that they can make informed decisions about genetic testing (NCCN v1. 2021; ACMG, 2015; ASCO 2013; ACOG, 2009; USPSTF, 2013)

Once a patient has been identified as an appropriate candidate for genetic testing, the testing options should be fully explained. It is imperative for the healthcare professional to explain why the test is being offered; what type(s) of testing is/are available, including the potential cost and insurance coverage issues; how the results might affect the patient's risk for cancer; what medical management options may be offered based on the results; and the importance of sharing results with family members (Table 2). Given the time it would take to explain all the nuances of every gene being tested on the multigene panels and possible medical management options, some providers have altered their counseling approach to a more global pretest education and a more tailored post-test discussion focusing on the actual results once they are available (Bradbury et al., 2015). While P/LPVs in *BRCA1* and *BRCA2* are responsible for most hereditary breast and ovarian cancer, other genes can influence risk for those cancers (Tung et al., 2016). Several publications have demonstrated that multigene panel testing yields findings likely to change clinical management for substantially more patients than does *BRCA1* and *BRCA2* testing alone (Desmond et al., 2015; Frey et al., 2017; Idos, et al., 2019; Pederson et al., 2018; Ricker et al., 2016; Rosenthal et al., 2017). Multigene testing has been shown to alter near-term cancer risk assessment and management recommendations for individuals found to carry P/LPVs across a broad spectrum of cancer predisposition genes (Desmond et al., 2015).

ASCO's Policy Statement on Genetic and Genomic Testing for Cancer Susceptibility (2003 and 2010 update) was created to guide the responsible integration of these new genetic and genomic technologies into clinical practice. In addition, the American College of Medical Genetics and Genomics (ACMG) has compiled 'Points to Consider in the Clinical Application of Genomic Sequencing' (Bush et al., 2018).

2.4 | Established models and published guidelines aid in estimating cancer risk and guiding medical management

P/LPVs in high- and moderate-risk breast cancer genes account for a portion of breast cancer risk; however, other factors can increase a woman's risk. These other factors include family history, reproductive history, lifestyle factors, and previous exposure to thoracic radiation. While having had previous breast biopsies is a marker for increased cancer risk, it is not, itself, a risk factor.

The risk for developing breast cancer can be calculated with various models that incorporate different variables (Table 1). These models typically provide short-term and long-term cancer risk estimates; however, each model has its strengths and limitations and must be considered in the context of the patient's personal and family history (Table 2). For example, some models can only be used for women after a certain age, others will not calculate risk for individuals with

TABLE 1 Comparison of models used to determine breast and/or ovarian cancer risk

Risk Model	Gail[a]	Claus[b]	BRCAPro[c,d,e]	Tyrer-Cuzick/IBIS[f,g]	CanRisk[h]	ASK2ME[i]
Variables Considered						
Personal history						
Current Age	✓	✓	✓	✓	✓	✓
Breast biopsies	✓			✓		
Breast biopsy: atypical ductal/ lobular hyperplasia	✓			✓		
Breast biopsy: lobular carcinoma in situ				✓		
Breast density				✓		
Breast cancer	*n*/a	*n*/a	✓	*n*/a	✓	✓
Ovarian cancer			✓		✓	✓
Pancreatic cancer					✓	✓
Prostate cancer					✓	✓
Age at menses	✓			✓		
Age at menopause				✓		
Age at first livebirth	✓			✓		
BMI (height and weight)				✓		
Use of HRT (type, years of use, since used)				✓		
Oophorectomy history			✓			✓
Race/ethnicity	✓		✓			
Ashkenazi Jewish ancestry			✓	✓	✓	✓
BRCA P/LPV status				✓	✓	✓
BRCA1 and *BRCA2*				✓	✓	✓
PALB2, *CHEK2*, *ATM*					✓	✓
Family history						
Age at diagnosis in relative with breast cancer		✓	✓	✓	✓	
1st degree females with breast cancer	✓	✓	✓	✓	✓	
2nd degree females with breast cancer			✓	✓	✓	
3rd degree relatives with breast cancer				✓	✓	
1st & 2nd degree unaffected relatives			✓	✓	✓	
3rd degree unaffected relatives			✓		✓	
1st & 2nd degree relatives with ovarian cancer			✓	✓	✓	
3rd degree relatives with ovarian cancer					✓	
Bilateral breast cancer in 1st degree relatives			✓	✓	✓	
Male breast cancer			✓		✓	
Pancreatic cancer					✓	
Prostate cancer					✓	
Variant status				✓	✓	
BRCA1 and *BRCA2*				✓	✓	
PALB2, *CHEK2*, *ATM*					✓	
Maternal & paternal family history		✓	✓	✓	✓	

[a]Gail et al., 1989.
[b]Claus et al., 1994.
[c]Parmigiani et al., 1998.
[d]Berry et al., 1997.
[e]Mazzola et al., 2015.
[f]Tyrer et al., 2004.
[g]Brentnall et al., 2015.
[h]canrisk.org, v1.0.4 (2020–01–14) (https://www.canrisk.org/) based on Antoniou AC, 2004.
[i]Braun et al., 2018.

a previous history of cancer, and some do not incorporate P/LPV status. Utilizing multiple models to present a range of risk, acknowledging those limitations, can be useful for clinicians and patients.

In addition to accessing these models from primary sources, platforms are available that integrate multiple models into one interface. Some can be utilized at no cost and others can be purchased with individual licenses. While neither the authors nor NSGC endorse any one model, platform or source in particular, clinicians can explore these programs to determine which, if any, might work in their own clinical settings. These platforms and software include, but are not limited to, CancerGene Connect (www.cagene.com), CancerIQ (www.canceriq.com), CRA Health (www.crahealth.com), and Progeny (www.progenygenetics.com) (Welch et al., 2018).

2.5 | Management recommendations should be based on clinical judgment, complemented by risk assessment, family history, and genetic test results (when appropriate)

Management of patients at increased risk for breast and ovarian cancer remains a challenge for healthcare professionals. Various guidelines and recommendations have been published regarding the management of patients considered to be at significantly increased risk for breast and ovarian cancer (Bevers et al., 2009; NCCN v1. 2021; Tung et al., 2020). Each of the recommendations has been based on literature reviews regarding the efficacy of various management options for individuals with P/LPVs, considering their personal and family history risk factors.

For appropriate patients, recommendations include surveillance as well as consideration of chemoprevention and risk-reducing surgeries, as summarized in Table 3. For example, screening MRI is recommended for women with a 20% or greater lifetime risk for breast cancer as determined by certain breast cancer risk models (Tyrer et al., 2004; Warwick et al., 2014), including those with a *BRCA* P/LPV, those with a strong family history of breast and ovarian cancer, and those who were previously treated with chest radiation for Hodgkin's lymphoma. In this high-risk population, studies have found a significantly improved sensitivity (71%–100%) for MRI compared with 16%–40% sensitivity with mammography (Saslow et al., 2007). Limited studies have not shown a statistically significant increased risk for ovarian cancer for families in which a *BRCA* P/LPV is not identified when the family history includes female breast cancer, but no cases of ovarian cancer (Metcalfe et al., 2009; Kauff et al., 2005). Therefore, in the absence of *BRCA* P/LPVs or a family history of ovarian cancer, there is no strong recommendation for risk-reducing bilateral salpingo-oophorectomy (RRSO) or screening for ovarian cancer.

Although research is exploring the penetrance of P/LPVs in non-*BRCA* hereditary ovarian cancer genes, the latest NCCN Guidelines list *RAD51C*, *RAD51D*, and *BRIP1* P/LPV carriers, in addition to *BRCA1*, *BRCA2*, and Lynch syndrome P/LPV carriers, as candidates for risk-reducing bilateral salpingo-oophorectomy (RRSO) at age 45–50 (NCCN v1. 2021). At the time of this publication, NCCN guidelines state that there is insufficient evidence to recommend RRSO in women who have P/LPVs in *ATM*, *NBN*, or *PALB2* and no evidence of increased ovarian cancer risk for *CDH1*, *CHEK2*, *NF1*. The rapid pace at which revisions are made to consensus guidelines requires providers to make concerted efforts to stay current, so that patients can be updated as needed to modify their care (Tung et al., 2020).

Recent data provide a new, although debatable, perspective on Lynch syndrome and suggest that individuals with *MSH6* and *PMS2* P/LPVs may present with a hereditary breast and ovarian cancer phenotype (Espenschied et al, 2017; Couch et al., 2017; Kurian et al., 2017; Roberts et al., 2018; Stoll et al., 2020). Given this possible association with a modestly increased risk for breast cancer, these genes may be considered when ordering a multigene panel for women with a personal or family history of breast cancer. However, current guidelines for women with MMR gene P/LPVs support average breast cancer screening guidelines, unless otherwise indicated by a personal or family history of breast cancer (NCCN Genetic/Familial High-Risk Assessment: Colorectal (NCCN v1. 2021).

Finally, long-term data support the association of an increased risk for prostate cancer, melanoma, and pancreatic cancer with *BRCA1* and *BRCA2* P/LPVs (Lowery et al., 2011). Currently, prostate cancer screening is supported for men with P/LPVs in *BRCA2*, starting at age 40 and can be considered for men with P/LP *BRCA1* variants (NCCN v1. 2021). Consensus guidelines support pancreatic screening in individuals with P/LVs in specific genes, including *BRCA1* and *BRCA2*, when there is a first- or second-degree relative with pancreatic cancer (Canto et al., 2013; Goggins et al., 2020; NCCN v1. 2021). No specific screening guidelines exist for melanoma, but general management, such as a full-body skin examination and minimizing exposure, is appropriate and may be further individualized based on cancers observed in the family (NCCN v1. 2021).

3 | POST-TEST CONSIDERATIONS

3.1 | Cascade testing

Identifying a P/LPV has familial implications. For families with a known P/LPV, cascade testing refers to the process of counseling and testing at-risk family members. Relatives who do not carry the variation can avoid unnecessary medical interventions, whereas those who do can pursue surveillance and prevention measures aimed at reducing morbidity and mortality (Lieberman et al., 2018). Clinicians should be able to identify which family members are at risk for inheriting the known variation and facilitate a discussion of their options for risk assessment and management (Alter; ACOG Committee Opinion No 727). In risk assessment for a known familial P/LPV, the clinician will also assess whether single-site or gene testing is clinically indicated, versus a full multigene panel test if family history or ancestry indicates there may be more than one P/LPV in the specific client. In addition, post-test genetic counseling for

TABLE 2 Strengths and limitations of breast and ovarian cancer risk prediction models

Model	Strengths	Limitations	Where to Access
Gail	• Online tool includes updates to more accurately estimated risk for African American women[1,2] and Asian and Pacific Islander women[3] • Used to determine eligibility for chemoprevention	• Only for women > 35 with no invasive breast cancer history • Limited family history, no 2nd degree relatives included • Paternal family history is not included • Age of diagnosis of family members not included • Does not include personal history of lobular carcinoma in situ • Not intended to determine eligibility for MRI screening • Risk estimates for Hispanic/ Latina women are subject to greater uncertainty • May underestimate risk for African American women with previous breast biopsies • Calculations for Native American and Alaskan Native are based on data from Whites	https://www.cancer.gov/bcrisktool/
Claus	• Includes ages of breast cancer diagnoses in family members • Includes various family history patterns	• No personal or hormonal risk factors included • Some family history relationship combinations are not given, but can be extrapolated • No independent validation • Data from White cohort	Tables from original manuscript https://doi.org/10.1002/1097-0142(19,940,201)73:3%3C643::AID-CNCR2820730323%3E3.0.CO;2–5
BRCAPro	• Allows for extensive family history of breast and ovarian cancers • Includes breast tumor pathology • Includes mastectomy and oophorectomy history	• No personal or hormonal risk factors included • Data from White cohort	BayesMendel package in R http://www4.utsouthwestern.edu/breasthealth/cagene/
BOADECIA CanRisk.org	• Allows for extensive family history of breast, ovarian, prostate, and ovarian cancers • Includes breast tumor pathology • Includes mastectomy and oophorectomy history • Includes non-*BRCA1/2* breast cancer predisposition genes • Can incorporate SNP level data	• No personal or hormonal risk factors included • Data from White cohort	http://ccge.medschl.cam.ac.uk/boadicea/ www.canrisk.org
Tyrer-Cuzick	• Integrates both personal and hormonal risk factors, as well as family history		http://www.ems-trials.org/riskevaluator/
ASK2ME	• For known P/LPV carriers only • Includes history of previous cancers and surgeries • Dynamic with continuous updates • Includes non-*BRCA1/2* cancer predisposition genes • Can generate output in various languages	• No personal or hormonal risk factors included • No family history included • Estimates may be based on one study, rather than meta-analyses • Dynamic with continuous updates	www.ask2me.com

Sources: Adams-Campbell et al., 2007; Gail et al., 2007; Matsuno et al., 2011.

individuals with P/LPVs should always include recommendations to refer relatives for their own genetic counseling/testing (Lieberman et al., 2018). Given the complexities of communicating information in families, clinicians should provide tools and resources that support individuals with a P/LPV in the dissemination of information (Riley et al., 2012). These aids can include family member letters, copies of genetic testing results, education and support websites, and referral information for genetics providers. Documentation of the known familial variant will help assure that at-risk family members are provided the appropriate genetic counseling and testing. Dissemination of information in families can be an evolving process; therefore, continued discussion with individuals who carry P/LPVs

TABLE 3 Recommendations for surveillance, chemoprevention and risk-reducing surgeries among high and moderate-risk individuals

	High-Risk Women	High-Risk Men	Moderate-Risk Women
Surveillance Options			
Annual mammography beginning at age 30 and breast MRI beginning at age 25.	✓		
Clinical breast exams, every 6–12 months, starting at age 20–25.	✓		✓
Annual breast MRI screening with contrast (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present, starting at age 25–29 (starting at age 20 in setting of TP53 mutation)	✓		
Annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast, age 30–75 Management should be considered on an individual basis over age 75	✓		
For women with a *BRCA* P/LPV who are treated for breast cancer but do not have bilateral mastectomy, screening should continue as described above with option of risk-reducing mastectomy if P/LPV is found in a high-risk gene, and considered for P/LPV in moderate-risk gene (such as ATM) in combination with family history.	✓		
Although unproven, annual or semiannual transvaginal ultrasound, pelvic exam and testing for serum CA–125 to screen for ovarian cancer beginning at 30 years of age should be considered until risk reducing bilateral salpingo-oophorectomy (BSO) is performed.	✓		
A benefit and risk discussion regarding annual digital rectal exams and prostate specific antigen (PSA) testing may be commenced at age 40 (per NCCN v.1. 2021): Prostate cancer screening for *BRCA2* carriers Consider prostate cancer screening for *BRCA1* carriers		✓	
Consider pancreatic screening based on *BRCA1/2* and other pancreatic-specific genes with P/LPVs and a first-degree or second-degree relative with pancreatic cancer or a very strong pancreatic cancer family history in the absence of a P/LPV, using endoscopic ultrasound or MRCP (per NCCN v1.2020)	✓	✓	
Consideration of annual mammography and breast MRI beginning at an age based on the earliest age of diagnosis in the family when a patient's empiric lifetime risk to develop breast cancer is at least 20%–25% as defined by risk models that are largely dependent on family history (e.g. Claus, BRCAPRO, Tyrer-Cuzick and BOADICEA) and not gene P/LPV status.			✓
Chemoprevention Options to Consider			
Medications such as tamoxifen, Raloxifene or aromatase inhibitors may reduce the risk of breast cancer.	✓		✓
Oral contraceptives (OCs) have been associated with up to a 45%–60% reduction in the risk of ovarian cancer in high-risk women (*BRCA1/2* P/LPV carriers).	✓		✓
Chemoprevention decreases the cancer risk when a patient's 5-year risk to develop breast cancer is greater than 1.66% as calculated by the Gail Model.			✓
Risk Reducing Surgical Options			
Risk reducing mastectomy may be considered depending upon the quality of screening (e.g. if the breasts are dense and difficult to read) or for women with significant concern about their risks. It reduces the risk of breast cancer by at least 90%. There is no standard recommended age at which this surgery should be performed across 'breast cancer genes'.	✓		✓
Counseling about risk-reducing mastectomy should always include: degree of protection, reconstruction options, and risks. Family history and residual breast cancer risk with age and life expectancy should be considered.	✓		✓
Risk reducing bilateral salpingo-oophorectomy (BSO)* is recommended between the ages of 35–40 or after childbearing. Because ovarian cancer onset in patients with *BRCA2* P/LPVs is an average of 8–10 years later than in patients with *BRCA1* P/LPVs, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with *BRCA2* P/LPVs.	✓		
Salpingectomy alone is not the standard of care for risk reduction, as women are still at risk for developing ovarian cancer.	✓		

(Continues)

TABLE 3 (Continued)

	High-Risk Women	High-Risk Men	Moderate-Risk Women
In premenopausal women, oophorectomy likely reduces the risk of breast cancer, but the magnitude is uncertain and may be gene-specific (consider in setting of newer genes such as *BRIP1*, based on family history).	✓		
For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA–125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35.	✓		

Source: NCCN, v1. 2021 (At the time of press, this version is most current. Updated versions have been published multiple times annually; for the most current guidelines, the reader may visit https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf).

may be necessary to address the needs and concerns that arise over the course of time.

It is also important to note that in some families, testing beyond the known P/LPV may be indicated. Even when a P/LPV has been previously identified, a review of family history is necessary, as families can harbor more than one P/LPV associated with hereditary cancer.

3.2 | Discussion of and management recommendations for secondary/incidental findings

In the absence of a known P/LPV, recommendations for cancer screening and prevention methods for patients and their family members are generally based on personal and/or family cancer history. However, as large-scale sequencing is now widely applied in clinical medicine, complicated issues have developed regarding the extent to which primary data, such as tumor profiling or whole-exome sequencing, should be analyzed and reported. When next-generation sequencing (NGS) is performed on tumor tissue, a tremendous number of genomic P/LPVs may be detected that may or may not be reflective of the germline. That tumor genomic information varies greatly with regard to relevance to the specific diagnostic and treatment questions. When P/LPVs are identified in genes outside of those considered part of the original purpose of the testing, they are considered secondary, or incidental, findings, and what to do with these P/LPVs has been a matter of considerable debate and discussion (ACMG Policy Statement, 2015; Presidential Commission for the Study of Bioethical Issues, 2013; Wolf et al., 2008).

ASCO recognizes that germline multigene panel testing is efficient for simultaneously evaluating multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. However, it may also identify P/LPVs in moderate or low-risk cancer genes or high-penetrance genes that would not have been analyzed on the basis of the personal or family history of the patient at hand (Robson et al., 2015). It is unclear whether identifying such low- to moderate-risk gene P/LPVs would have much impact on individual clinical management recommendations for patients who have a clinically significant personal or family history of cancer (Desmond, et al., 2015).

There has been little consensus as to which genes should be included on panels offered for cancer-susceptibility testing, with some centers (or laboratories) offering large, very comprehensive panels and others constraining their offers to small, targeted panels of genes with actionable results. There may be uncertainty regarding accurate risk estimates and management strategies for families with unexpected P/LPVs in high-penetrance genes when there is no evidence of the associated syndrome in the family.

Many panels also include moderate-penetrance genes; based on published literature, P/LPVs in these genes increase the risk of cancer two- to fivefold, which may also be affected by factors such as family history. It is not always clear whether the medical management of individual patients or their family members should be altered based on the presence or absence of a moderate-risk P/LPV, and therefore, the clinical utility of testing for moderate-penetrance variants is also vague (Robson et al., 2015). Additionally, variants of uncertain significance are quite common, but have no immediate clinical utility, and determining whether they are functionally significant can be quite challenging (Robson, 2014). Commercial laboratories are decreasing traditional follow-up studies, such as segregation analysis for these findings, due at least in part to the statistical complexity of proving pathogenicity given incomplete penetrance. In contrast to accepting a sample from any member of the family of interest, most laboratories are requesting additional family history information and then carefully selecting which specific individual(s) in the family would be most informative to aid in understanding the variant of interest.

Pretest genetic counseling has long been recommended to facilitate informed decision-making and discuss possible outcomes with patients undergoing genetic testing since 1996, and is recommended for those undergoing panel-based testing. Possible outcomes of these types of results include (a) inappropriate medical intervention, (b) psychological stress regarding incidental identification of a P/LPV in a gene that was not suspected by family history, and (c) medical management of moderate-penetrance P/LPVs that is not evidence-based (Lu et al., 2014; Robson et al., 2010; Statement of the American Society of Clinical Oncology, 1996). It is vital in pretest counseling to highlight the purpose of the testing as well as the potential outcomes and implications of the various results for patients and their family members. Although it is generally not practical to review each of the genes in a panel individually, it is helpful to discuss the difference between well-described high-penetrance genes

and less well-understood moderate-penetrance genes (Robson et al., 2015) and to engage the patient in decision-making around what type of test (e.g., single-gene, large panel) suits his/her wants and needs. Recent studies have suggested that electronic genetic education and subsequent results disclosure without genetic counseling does not increase patient distress and leads to higher test uptake (Swisher et al., 2020). However, this does not negate the potential medical mismanagement discussed above.

The future path for research and clinical translation depends on the better understanding of actionable P/LPVs and the development of an evidence base to support the disclosure of incidental findings. In order to do this, decision tools need to be created, as well as the clinical capacity to provide genetic counseling related to incidental and uncertain findings, for which there are no standards of care (Bombard et al., 2013; Slavin et al., 2015). These will best be formulated by the genetics professionals caring for affected patients and their family members.

3.3 | Discussion of reproductive risks

For individuals of reproductive age with P/LPVs, counseling about options for prenatal diagnosis and/or assisted reproduction, including pre-implantation genetic testing (PGT), is important. Utilization of genetic test results for reproductive decision-making may include the use of donor gametes, adoption, and PGT. The discussion should include an introduction to the known risks, limitations, benefits, and costs of these technologies. Future discussions may be necessary to address an individual's changing needs, and a referral to centers with specialty in these technologies should be facilitated for those who express interest.

Many multigene cancer panels include genes that are associated with rare autosomal recessive conditions that are manifested when a P/LPV in that gene is inherited from both parents (i.e., in the homozygous state). This includes, but is not limited to: ataxia telangiectasia, caused by biallelic *ATM* P/LPVs; Fanconi anemia, caused by biallelic P/LPVs in *BRCA2*, *BRIP1*, *RAD51C*, *RAD51D*, or *PALB2* genes (among others not commonly encountered on breast/ovarian cancer gene panels); Nijmegen breakage syndrome, caused by biallelic P/LPVs. in *NBN*; and constitutional mismatch repair deficiency (CMMRD), resulting from biallelic P/LPVs in mismatch repair genes associated with Lynch syndrome (Rainville et al., 2020; Walsh et al., 2017; Wimmer et al., 2014). Individuals who carry P/LPVs in these genes should be informed of this risk, as it may aid reproductive decision-making for themselves and/or family members, and requires a discussion of genetic testing of the same gene in their partners (Mets et al., 2016; Offit et al., 2003).

3.4 | Testing and treatment issues

Many academic and commercial laboratories now offer DNA sequencing of tumor tissue, or of circulating tumor DNA, to detect somatic variants that may be used for targeting oncologic treatments. Tumors in certain individuals with P/LPVs respond differently to chemotherapeutic agents, such as poly-ribose ADP polymerase (PARP) inhibitors, based on exploiting their differences in DNA repair. Despite standard treatments for some aggressive cancers (e.g., ovarian, prostate, pancreatic, and breast), there remains a significant need for targeted therapies to improve clinical outcomes in recurrent cancers. The most promising targeted therapies so far include antiangiogenic agents and PARP inhibitors (Papa et al., 2016). PARP inhibitors are specifically active in cells that have impaired DNA repair in the homologous recombination (HR) pathway. Cells with altered *BRCA* and other breast and ovarian cancer-causing genes (e.g., *ATM*, *CHEK2*, *PALB2*) have HR deficiency. The use of targeted therapies in the treatment of several cancers, both as monotherapies or in combination, has been identified and approved by the FDA. In addition, clinical trials of a range of targeted therapies are ongoing, such that selection of therapeutic agents and appropriate patient populations will allow strategic application of targeted therapeutics (US FDA, Vetter & Hays, 2018).

The Food and Drug Administration (FDA) has approved a variety of PARP inhibitors, such as olaparib, niraparib, talazoparib, and rucaparib, for the treatment of *BRCA*-associated metastatic breast, ovarian, prostate, fallopian, peritoneal, and pancreatic cancer (Patel et al., 2020). This has created an even more compelling reason to systematically integrate genetic testing into clinical practice, as knowledge of genetic status may impact treatment decisions (Kaufman et al., 2015; Swisher et al., 2017; US FDA, 2018, US FDA).

The incorporation of simultaneous germline and somatic tumor testing is growing in oncology. In the tumor tissue or cells, inherited genetic variants as well as somatic variants will be present in the DNA sequence. Therefore, P/LPVs identified in tumor cells could represent germline P/LPVs, and these may have implications for future cancers as well as risks to family members. It is imperative for clinicians ordering tumor DNA sequencing to consider whether identified variants are likely to represent germline P/LPVs, as these need to be confirmed using germline samples. This is especially important considering that nearly 10% of patients with advanced cancer may have actionable, germline P/LPVs that would not have been found using current guidelines for clinical testing (Mandelker et al., 2017). Thus, patients with P/LPVs in tumor tissue should be referred to genetic specialists for counseling and germline testing (Giri et al., 2017). Simultaneous sequencing of tumor-normal DNA reveals inherited cancer predisposition P/LPVs in 3%–12.6% of pediatric and adult patients with cancer (Meric-Bernstam et al., 2016; Schrader et al., 2016; Seifert et al., 2016; Meric-Bernstam et al., 2015; Zhang et al, 2015).

Mandelker et al conducted a prospective analysis to determine the incremental proportion of P/LPVs detected by concurrent germline analysis in patients with advanced cancer undergoing universal tumor profiling. This is compared with selective germline testing, based on existing practice guidelines, which factor in personal and/or family history. Of the 1,040 patients, 17.5% had P/LPVs indicating a cancer susceptibility, and 9.7% would not have had these variants detected using current NCCN testing guidelines. Most notably, 38 patients (3.7%) of these germline findings resulted in a change to targeted therapy,

including six for whom a genetic evaluation would never have been done based on current guideline-based testing. Clinicians should be aware of whether tumor, germline, or both have been conducted, and adequately interpret this information for patients (Mandelker et al., 2017). The threshold for determining the clinical estimating significance of a variant finding is expected to be different for somatic versus germline assays. Therefore, clinicians utilizing somatic assays should be aware of these differences in order to recognize and investigate specific research somatic variants, and will fall to the clinician to determine whether a somatic VUS finding should trigger a germline workup if its presence in the germline would alter proposed management.

Current NCCN guidelines reflect this and recommend that any individual, at any age, who is found to have a P/LPV in a cancer-susceptibility gene on tumor testing be referred for genetics evaluation (NCCN v1. 2021). Conversely, it is important to note that the absence of a P/LPV on a tumor test does not rule out a germline variant, and individuals with 'normal' or 'negative' tumor testing should still undergo germline analysis if they meet established criteria or clinical suspicion of hereditary cancer.

In the case of a germline VUS, patients should be managed based on personal and family history. Individualized management may include increased surveillance and possibly other interventions, such as surgery or chemoprevention, depending on their history rather than the test result. Typically, family members are not tested for the VUS, because of the lack of understanding of its clinical implications. Most variants of uncertain significance are ultimately reclassified as either benign or likely benign. However, some VUSs will be reclassified as pathogenic or likely pathogenic, and patients should be re-contacted for a discussion about the cancer risks for them and their family members based on the new classification (Bombard et al., 2019; Easton, Deffenbaugh, et al., 2007; Macklin et al., 2018; Slavin et al., 2018). Procedures and policies in current healthcare systems regarding re-contacting patients are challenging. Ideally, it is a shared responsibility between healthcare providers, laboratories, and patients, respecting previously obtained patient consent (Policy Statement of the ACMG Social, Ethical, & Legal Issues Committee, 1999; Carrieri et al., 2019).

3.5 | Provision of patient resources

A genetics consultation should include the provision of patient resources, including scientific information, psychosocial support, financial assistance programs, and advocacy. Personalized medicine creates the demand and responsibility of educating patients about their diagnoses and the resources they may use to address them. The provider of the diagnosis of a *BRCA1* P/LPV, for example, has the duty to educate the patient about support and informational resources, as appropriate to the individual. The majority of individuals who undergo genetic testing and are found to carry a P/LPV do not suffer long-term psychological distress. However, there may be individuals for whom the impact of this information has a long-term impact and providers should be attentive to those patients' needs and provide referrals to appropriate mental health and support resources (Braithwaite et al., 2004; Meiser, 2005).

While most insurance companies provide coverage of genetic testing for appropriately selected individuals, this coverage may vary. However, for patients who have limited or no insurance coverage, many major testing laboratories offer financial assistance programs and providers should be aware of such resources so that genetic testing can be accessed more equitably. After testing, the clinician should provide appropriate downstream referrals to specialists, as many institutions and health plans do not have familiarity with appropriate resources other than those for *BRCA1* or *BRCA2* carriers.

3.6 | Ethical, legal, and social implications of genetic information and testing

As with all genetic testing, HBOC testing has the potential to raise ethical, legal, and social issues, both within the family and for society as a whole. A variety of concerns has been expressed with respect to predisposition testing for less than fully penetrant genes, as well as the potential for prenatal testing or testing of minors for adult-onset conditions. Additionally, patients may express concern about the potential for genetic discrimination, particularly with regard to health and life insurance in the event of a positive test result. Almost all states have enacted laws regarding genetic discrimination for health insurance plans, and many states have stringent rules regarding employment discrimination based on genetic testing (Greely, 2005). In addition, there are federal regulations in place that speak to workplace and health insurance discrimination. Regardless of this legal reassurance, it is important that clinicians recognize and appropriately address the issues of disclosure of information, federal and state protections, and confidentiality with their patients (Fasouliotis & Schenker, 2000; Genetic Information Nondiscrimination Act of 2008 (GINA); ; ; (Pub. L. No. 110–223); Health Insurance Portability & Accountability Act of, 1996 (HIPAA); Americans with Disabilities Act of 1990 (ADA). The fear of discrimination may prevent at-risk individuals from having genetic testing, which in turn could have significant health implications (Greely, 2005). Counseling regarding the ethical and legal challenges raised by HBOC testing should also be guided by the overall ethical code of the National Society of Genetic Counselors (NSGC Code of Ethics, adopted 1/92, revised 4/17, NSGC.org). It is worth remembering that privacy and confidentiality are not a foregone conclusion in the direct-to-consumer testing marketplace, and a consumer cannot expect the same protections if genetic testing occurs outside of the traditional clinical setting. Risk assessment and screening practices are complex, and this document is not meant to address all the nuances for various patient populations in all circumstances.

4 | CONCLUSIONS

The process of cancer risk assessment and genetic counseling for HBOC requires multiple steps, including:

- Gathering personal medical and family history data
- Psychosocial assessment and referral if indicated
- Education focused on basic principles of genetics and cancer
- Discussion of cancer and P/LPV risk and how personalized risk estimates are derived
- Facilitation of the informed consent process through discussion of the risks, benefits, limitations, and likelihood of identifying a P/LPV
- Results disclosure (if applicable)
- Discussion of medical management options
- Discussion of the familial implications of testing and dissemination of information
- Review of issues related to genetic discrimination

A growing number of non-genetics experts are having conversations with patients about their cancer risk, prevention approaches, early detection, and personalized medical management options. It is clear that the more healthcare providers working together to identify patients at risk for hereditary breast and ovarian cancer, the better the delivery of personalized cancer risk assessment and testing. Genetics professionals have a distinctive skill set that complements and augments the care that individuals at risk for hereditary breast and ovarian cancer receive from their physicians. The above recommendations provide a best practices approach to offering a uniform delivery of comprehensive care for families and individuals with hereditary breast and ovarian cancer.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work as well as significant efforts in drafting the work or revising it critically for important intellectual content. All authors agree to be accountable for all aspects of the work in insuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors provided final approval of the version to be published.

COMPLIANCE WITH ETHICAL STANDARDS

The author group composition is in compliance with the National Society of Genetic Counselors Practice Guidelines Committee Conflict of Interest Policy. This policy requires all proposed authors to disclose conflict of interest prior to selection and imposes thresholds for conflict of interest with the potential for direct, personal financial benefit, or other real or perceived conflict of interest,

CONFLICT OF INTEREST

Shelly A. Cummings is employed by and has stock in Myriad Genetics, Inc., a diagnostic genetic testing laboratory that offers genetic testing for hereditary cancer syndromes. Janice L. Berliner, Brittany Boldt Burnett, and Charité N. Ricker declare that they have no conflicts of interest.

HUMAN STUDIES AND INFORMED CONSENT

No human studies were carried out by the authors for this article.

ANIMAL STUDIES

No non-human animal studies were carried out by the authors for this article.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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