Prevention and Screening in Hereditary Breast and Ovarian Cancer

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Here we review current guidelines on breast and ovarian cancer screening, prophylactic surgery, and other risk-reduction strategies in patients with these mutations, and we detail the data that drive these recommendations.

Introduction/Background

With 246,660 new diagnoses and 40,450 deaths projected for 2016, breast cancer remains the most commonly diagnosed cancer among women in the United States.[1] Despite a substantial improvement in overall survival (OS) for patients with metastatic breast cancer over the past 20 to 30 years, it is still the second leading cause of cancer-related deaths in the United States. Meanwhile, ovarian cancer—with 22,280 new diagnoses and 14,240 deaths projected for 2016—is considerably less common but is associated with much higher mortality. Because of nonspecific presenting symptoms and the lack of an effective screening test, ovarian cancer is often diagnosed at an advanced stage (III or IV) and is associated with a poor 5-year OS (stage III: 40%–60%; stage IV: 17%), which has remained relatively unchanged over the past 30 years.[2] Although only 5% to 15% of breast or ovarian cancers are associated with a previously identified hereditary syndrome, the number increases to 20% to 40% when patients are found to have validated risk factors, such as Ashkenazi Jewish ethnicity or a family history of breast or ovarian cancer.[3]

Germline mutations in several genes have been shown to predispose patients to breast and/or ovarian cancer (Table 1), and these genes can be categorized based on the level of penetrance and phenotypic expression.[4-12] Most high-penetrance genes are associated with well-described genetic syndromes and have defined cancer and associated health risks and clear medical management guidelines. Moderate- to low-penetrance genes and genes more recently found to be associated with hereditary breast and/or ovarian cancer risk may have less well-defined clinical profiles and lack consensus-based management guidelines.
Beginning in 2012, next-generation sequencing became commercially available within the United States and replaced the Sanger sequencing technique because of its ability to analyze multiple sequence reads per base pair (as opposed to single sequence reads per base pair with Sanger sequencing).[13] The incorporation of next-generation sequencing into clinical practice increased the options for and availability of genetic testing and, in some cases, helped redefine the phenotypes of hereditary syndromes. Then in mid-2013, the US Supreme Court ruled to strike down the *BRCA* gene patent. The Supreme Court ruling, coupled with the rise of next-generation sequencing, rapidly made genetic testing for hereditary breast and ovarian cancer more affordable, more widely available and sought after by patients, and more comprehensive in its scope.
In this review, we look at the incorporation of genetic testing for hereditary breast and ovarian cancer into clinical practice. Specifically, we focus on screening, risk modifications, surveillance, risk reduction and treatment strategies, ethical and counseling issues, and the challenges inherent in interpreting a large amount of genetic information and applying it in clinical practice.

Indications for Genetic Services

According to guidelines issued by the National Comprehensive Cancer Network (NCCN) and supported by other medical societies, genetic testing for hereditary breast and/or ovarian cancer syndromes is currently recommended for the following patients:
1) Those with breast cancer diagnosed at or before age 45 years.
2) Those with triple-negative breast cancer diagnosed at or before age 60 years.
3) Patients who have two or more primary breast cancers.

4) Patients with invasive ovarian, fallopian tube, or primary peritoneal cancer.
5) Male patients with breast cancer.
6) Ashkenazi Jewish patients with breast cancer, regardless of age.
7) Patients who have breast cancer and a first-, second-, or third-degree relative with breast cancer diagnosed before age 50 years.
8) Patients with breast cancer who have two or more relatives with breast cancer diagnosed at any age.
9) Patients with breast cancer who have a first-, second-, or third-degree relative with ovarian cancer.
10) Patients with breast cancer who have a relative with male breast cancer.
11) Breast cancer patients who have two or more first-, second-, or third-degree relatives with pancreatic and/or prostate cancer.[14-16]
However, guidelines change frequently based on the acquisition of new data and reanalysis of older studies, and different medical societies often have slightly different recommendations for particular clinical scenarios. Therefore, it is always advisable to recommend genetic counseling for patients when clinical suspicion of a hereditary syndrome is present. Genetic counselors can explain the risks and benefits of testing and can also explore with the patient whether testing is warranted, given their particular clinical and family history, and whether their insurance plan will cover testing (so that they can be aware of possible out-of-pocket costs).
Approximately 1 in 40 patients of Ashkenazi Jewish descent has one of three founder *BRCA* mutations, which account for 90% of hereditary breast and/or ovarian cancer in this population (185delAG, 5382insC [*BRCA1*]; and 6174delT [*BRCA2*]).[17] Nine different *BRCA* mutations account for 53% of cancers in the US Hispanic population; the most common is 185delAG.[18] Among a group of people in Iceland, a founder mutation (999del5 [*BRCA2*]) occurs in approximately 8% of patients with female breast cancer, 40% of those with male breast cancer, and 6% of those with ovarian cancer.[19] Among a group of French Canadians, six *BRCA* founder mutations account for 75% to 85% of hereditary breast and/or ovarian cancers.[20]
In addition to guidelines and a comprehensive family background assessment, other commonly employed methods of assessing the risk of hereditary breast or ovarian cancer include quantitative risk assessment tools such as the BRCAPRO, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, the Tyrer-Cuzick tool, the Claus model, and the National Cancer Institute's Breast Cancer Risk Assessment Tool.[21]

Choosing a Platform for Testing

Once it is determined that a patient is at high risk for hereditary breast and/or ovarian cancer and that the benefits of testing outweigh potential harms, various commercially available genetic testing platforms are often used. Table 2 provides a comprehensive description of some of the most widely used platforms, but because many different laboratories (eg, Myriad, Ambry, Invitae, and GeneDX) offer similar options for testing, it is not an all-inclusive list. These different testing options are heterogeneous with regard to cost, insurance coverage, financial assistance options, ease of use, laboratory reliability, turnaround time, accuracy, number of genes tested, and rate of obtaining at least one genetic variant of unknown significance (VUS). For this reason, we strongly suggest that testing be performed after a discussion with a certified genetic counselor, who can explain the risks and benefits of each approach and tailor the decision to the patient's specific needs.
There are a number of different options to choose from. For example, the Integrated BRACAnalysis™ (Myriad) is a syndrome-specific panel that checks exclusively for germline *BRCA1/2* mutations, has a short turnaround time, is associated with low rates of obtaining a VUS, and produces results for which there are evidence-based guidelines for their clinical application. New "guidelines-based" panels such as Ambry's BRCAPlus Expanded™ look not only for germline *BRCA1/2* mutations but also at genes such as *ATM*, *CHEK2*, and *PALB2*, for which guidelines suggest that enhanced breast screening with magnetic resonance imaging (MRI) would be recommended. Finally, there are broader tests, such as BreastNext™ (Ambry); this cancer-specific gene panel tests for both clinically actionable gene mutations for which there are clear cancer risks and management guidelines (high penetrance) and those genes for which there is uncertainty regarding cancer risk, age of diagnosis, spectrum of associated tumors, and medical management (moderate penetrance). Myriad's MyRisk™ is another more comprehensive cancer panel that tests for high- and moderate-penetrance genes associated with multiple cancer types. It is commonly used in patients who have a complex family history with multiple cancer types; however, it is also associated with a greater likelihood of

obtaining a VUS and with uncertainty regarding genes that have moderate penetrance. Currently, there are no guidelines regarding which panel to use in each particular clinical circumstance. However, for patients without a mutation, those with VUS–likely benign, and those with VUS, medical management is typically based on personal and family cancer history. Meanwhile, for those patients with VUS–likely pathogenic and those with a mutation, medical management is typically based on cancer risks associated with the gene in which the mutation was found.

Population-Based Screening?

Recently, there has been interest in population-based screening rather than family history–based screening for *BRCA* founder mutations, particularly in populations with a high percentage of persons of Ashkenazi Jewish descent. A randomized controlled trial performed in the United Kingdom looked at testing for *BRCA* founder mutations in either all Ashkenazi Jewish women older than age 30 years *or* only those with a strong family history.[22] The researchers found that population-based screening identified up to 56% of additional mutation carriers and did not affect short-term psychological or quality-of-life outcomes significantly. Similarly, an Israeli study simulated population-based screening by identifying families that harbor *BRCA* mutations by screening healthy Ashkenazi Jewish males recruited from outpatient clinics.[23] The investigators then enrolled their female relatives and found high cancer risks in mutation carriers identified this way, regardless of family history. They therefore concluded that population-based screening might identify a significant number of carriers not identified by family history criteria and might lead to concrete improvements in cancer prevention for these patients.

In view of these data, there has been a push in the United States toward universal screening for Ashkenazi Jewish populations, with programs that offer subsidized testing for the three *BRCA* founder mutations for persons of Ashkenazi Jewish descent regardless of family history.[24] There is still a great deal of controversy over universal screening for the general American public, given the low prevalence of deleterious mutations (the overall prevalence of *BRCA1* mutations is estimated at 1 in 300 and *BRCA2* at 1 in 800[15]) and the high risk that a VUS will be found.[25]

Penetrance/Cancer Risk Modifiers

For *BRCA1* mutation carriers, the cumulative risks of breast and ovarian cancer by age 70 years vary by study, but are approximately 57% and 40%, respectively.[26] For *BRCA2* mutation carriers, the cumulative risks are 57% and 18%, respectively. *BRCA* mutation carriers are also at increased risk for a second primary breast cancer; male breast cancer (*BRCA2*: 8% lifetime risk); prostate cancer (fivefold to ninefold increase); pancreatic cancer (twofold to fourfold increase); skin cancer (melanoma); and endometrial, gastric, and biliary cancers.[27] Mutations that occur within the central region of the *BRCA2* gene, called the ovarian cancer cluster region (nucleotides 4075–6503), compared with those in the 5´ or 3´ region, may be associated with a significantly decreased risk of breast and prostate cancer in male mutation carriers but a significantly higher risk of ovarian cancer in women.[17] Differences in the penetrance of gene mutations associated with increased breast cancer risk may be attributable to small nucleotide polymorphisms (SNPs) and higher SNP aggregate scores. Among *BRCA1* or *BRCA2* mutation carriers, two SNPs (chromosome 5p12) have been associated with an increased risk of estrogen receptor–positive breast cancer,[28] and additional research will likely lead to the identification of additional modifiers of *BRCA1/2* expression in the future.

Aside from genetic risk factors, the following have been established as risk factors for breast cancer: a family history of breast cancer in first-degree relatives, older age, young age at menarche (< 12 years), older age at first birth (> 30 years), older age at menopause (> 55 years), use of oral contraceptives, use of hormone replacement therapy, alcohol (2 to 5 drinks per day), ≥ 75% breast density on mammography, and a history of atypical hyperplasia on biopsy. The following factors have been shown to increase the risk of breast cancer in women with *BRCA1* and *BRCA2* mutations: use of oral contraceptives (*BRCA1* and *BRCA2*) and smoking (*BRCA2*). Meanwhile, the following factors have been shown to decrease the risk of breast and ovarian cancer: alcohol consumption (*BRCA1*), breastfeeding (*BRCA1*), and late age at menarche (*BRCA1*).[26] Finally, a number of other genetic syndromes predispose to breast cancer, ovarian cancer, and other tumor types (see Table 1).

Breast and Ovarian Cancer Prevention

Screening

Although several medical societies issue regularly updated screening guidelines related to hereditary breast and ovarian cancer, these guidelines are not 100% sensitive or specific and cannot take into account all of the possible clinical circumstances. Therefore, a personalized approach that takes into account individual and family medical history, as well as published screening guidelines, is required.
Female breast cancer. According to the NCCN guidelines, the major breast cancer screening and prevention recommendations for unaffected female *BRCA* mutation carriers are as follows: 1) breast awareness starting at age 18 years; 2) clinical breast examination every 6 to 12 months beginning at age 25 years; 3) annual breast MRI scan from ages 25 to 29 years; 4) annual mammogram and breast MRI scan from ages 30 to 75 years; and 5) consideration of chemoprevention and risk-reducing mastectomy.[14] The United Kingdom's National Health Service cancer screening program offers similar guidelines for this patient population: 1) breast MRI every year starting at age 25 years; 2) mammography every 18 months between ages 40 and 49 years; and 3) mammography every 3 years starting at age 50 years.[29]
Given the concern about radiation exposure in women with an *ATM* mutation, such women are encouraged to undergo annual MRI breast screening beginning at age 25 years.[12] Mammography should be performed every 18 months between ages 40 and 49 years, and then every 3 years starting at age 50 years.
Although mammography is often indicated at earlier ages for carriers of high-risk mutations, its sensitivity for detecting breast cancer is lower in these women than in the general population (differences in breast density and the risk of cancers developing during the interval between mammograms are the primary reasons for this). Although the incorporation of breast MRI into the screening of genetically high-risk patients has not been shown to improve patient OS, it has increased cancer detection rates and the percentage of patients in whom early-stage disease is diagnosed. In this patient population, when mammography and MRI are used concurrently, the combination is more sensitive and specific for detecting breast cancer than either modality alone.[30]

TO PUT THAT INTO CONTEXT

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What Did Screening for Familial Breast and Ovarian Cancer Syndrome Entail Until Recently?
When it was discovered that mutations in the *BRCA* genes are responsible for the majority of cases of familial breast and ovarian cancer syndrome more than 20 years ago, there was an enormous sigh of relief. For the first time, individuals from high-risk families could be tested and preventive intervention could be undertaken in the people most likely to benefit. The guidelines on whom to test were relatively straightforward, and when carriers were identified, intervention was easy to recommend because the risk of disease was deemed significant, likely owing to the fact that the original families tested were at the highest risk, probably because of high gene penetrance.
What Developments Have Made Care of At-Risk Patients More Complicated in Recent Years?
Needless to say, as highlighted in this review by Zeichner et al, things have become a lot more complicated. First, as the indications for testing have become broader, it has become clear that *BRCA* mutations can be found in families where the prevalence of disease is much lower than what

was originally observed, likely as a result of inheritable cofactors that influence gene penetrance. Sometimes the explanation is that there are few female relatives within a kindred. Still, how does one handle a positive *BRCA* test result in a family where the incidence of cancer is very low? Also, an increasing number of lower-risk gene mutations are being identified, and quantitating the associated risk is challenging, at least without additional information. Finally, the number of genetic tests and the number of companies performing these tests seem to be increasing on a daily basis.

How Should Persons Possibly at Risk for Hereditary Breast or Ovarian Cancer Be Managed Now?

For the foregoing reasons, it is more important than ever for patients considering testing to be evaluated by an experienced genetics team, who can both assist with choice of test as well as provide optimal counseling when results become available. Hopefully, in the future we will be able to more accurately quantify risk based on all the relevant factors in a particular individual and fulfill the promise of “personalized medicine” that we hear so much about. Until then, it is important to partner with the most experienced experts and make use of the best resources available so as to best serve our patients.

Ovarian cancer. Several physical examination findings, patient symptoms, biomarkers, and radiographic modalities have been tested for the screening of women for ovarian cancer. The ovarian symptom index (OSI) was developed. Women are considered to have a positive index score if they report pelvic or abdominal pain, bloating, increased abdominal size, or early satiety that occurs more than 12 times a month for less than 1 year.[31] In a study of women at high risk for ovarian cancer, the combination of the OSI and cancer antigen 125 (CA-125) level identified more cancers than CA-125 level alone.[31] However, the OSI had very low specificity and low positive predictive value (PPV). In addition, CA-125 is elevated in only 50% of women with early-stage disease[32] and in approximately 1% of healthy women,[33] and levels can vary considerably with ethnicity, smoking status, menstrual cycle, and age.[34]

A prospective study of asymptomatic postmenopausal women found that an elevated CA-125 level (≥ 30 U/mL) was a powerful predictor of subsequent ovarian cancer risk (1-year relative risk: 35.9%; 5-year relative risk: 14.3%), but annual CA-125 measurements in an average-risk population had very low specificity. Combining age-specific incidence of cancer and absolute CA-125 level and its rate of change over time improved sensitivity for detection of ovarian cancer to 62%–86%, with a 98% fixed specificity.[35] Three large screening studies showed a 99% specificity and 3% PPV for the use of a single CA-125 level for detection of ovarian cancer in postmenopausal women.[36-38] In a randomized controlled trial of ovarian cancer screening with transvaginal ultrasonography (TVUS) and CA-125 vs usual care, the combination of annual CA-125 measurement and TVUS was associated with a 3.7% PPV for ovarian cancer (2.6% at 4-year follow-up).[39,40]

Human epididymis protein 4 (HE4) appears to have similar sensitivity to CA-125 as a biomarker for ovarian cancer. In a study of 531 women with pelvic masses, an algorithm that used HE4 and CA-125 correctly classified 93.8% of high-risk ovarian cancer cases.[41] A commercial assay for serum HE4 is available (the ARCHITECT HE4 test, Abbott Laboratories) but is currently approved by the US Food and Drug Administration only for monitoring women with ovarian cancer for disease recurrence or progression. TVUS has been evaluated as a potential first-line screening method for ovarian cancer, with high sensitivity (75%–100%), specificity (94%–99%), and PPV (2.8%–8.9%). However, in a group of unselected postmenopausal women, after 11 years of follow-up there was no significant mortality reduction compared with no screening.[42] In another study, when screening with TVUS was performed annually in women with a family history of ovarian cancer, it was found that 70% of the screen-detected cancers were either stage I or II and associated with a 5-year OS rate of 84.6% (vs an OS rate of 53.7% for cancers found in unscreened women).[43] Despite the paucity of strong evidence that screening improves survival, the NCCN recommends that women with identified hereditary ovarian cancer syndromes undergo screening every 6 months with CA-125 measurement and TVUS beginning between the ages of 30 and 35 years or 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family.[14] Meanwhile, the US Preventive Services Task Force has recommended against screening for ovarian cancer and has stated that the potential harms of general population screening for ovarian cancer outweigh any potential benefits.[44]

Risk Reduction

Although chemoprevention or risk-reducing mastectomy is generally recommended for all women who are carriers of mutations that place them at high risk for breast cancer, decisions are by

necessity highly individualized and place emphasis on a particular woman's type of mutation and her personal and family cancer history. For example, women with *BRCA* mutations should be offered prophylactic bilateral mastectomy, whereas those with *CHEK2* mutations (in whom more slow-growing, predominantly estrogen receptor–positive breast cancers are more likely to develop) may be better candidates for chemoprevention. Although the NCCN recommends that *BRCA* carriers be offered prophylactic bilateral mastectomy,[14] the decision about whether to undergo surgery is based on personal preference, given that effective screening is available.

Risk-reducing or prophylactic bilateral mastectomy has been shown to decrease the incidence of breast cancer by as much as 90% in patients at risk for hereditary breast cancer.[45] In a large, prospective, multi-institutional study of women with known *BRCA* mutations, breast cancer developed in none of the patients who had a risk-reducing mastectomy compared with 98 of those who did not undergo the procedure (0/247 vs 98/1,372).[46] Women who declined mastectomy were offered increased surveillance, which included annual mammography and MRI. It is recommended that patients who opt to proceed with surgery undergo a bilateral total mastectomy rather than a subcutaneous mastectomy because the latter spares more glandular tissue, which could be a nidus for future cancers. Owing to its superior cosmetic results, skin-sparing mastectomy with or without preservation of the nipple-areolar complex, followed by immediate breast reconstruction, is increasingly being performed.[47]

Studies have demonstrated that bilateral salpingo-oophorectomy (BSO) reduces ovarian and breast cancer incidence and mortality in premenopausal women and reduces ovarian cancer incidence in postmenopausal women.[47] For mutation carriers who have not undergone BSO, the NCCN recommends ovarian cancer screening with concurrent TVUS (on days 1 to 10 of menstrual cycle) and CA-125 measurement (after day 5 of menstrual cycle) every 6 months beginning at age 30 years or 5 to 10 years before the earliest age of first ovarian cancer diagnosis in the family.[14] For *BRCA* mutation carriers, risk-reducing BSO is recommended for women who have completed childbearing; surgery should ideally be performed by age 35 to 40 years. BSO is associated with a 70% to 80% reduction in risk of ovarian cancer (*BRCA1*), a decreased risk of breast cancer (*BRCA1* and *BRCA2*), and a decreased all-cause mortality, with a trend toward decreased ovarian and breast cancer–specific mortality.[48] Evidence suggests that even short-term use of modern oral contraceptive pills in *BRCA* mutation carriers decreases the risk of ovarian cancer[49]; however, oral contraceptives may also increase the risk of breast cancer in women who take them continually for 4 to 5 years and start taking them before age 20 years or before their first pregnancy.[50]

Prevention of Other Cancers

Limited information suggests that *BRCA* mutation carriers are not at increased risk for endometrial cancer; therefore, no national guidelines exist regarding hysterectomy at the time of BSO in *BRCA* carriers. However, a recent multicenter study that prospectively followed women with *BRCA1* mutations who underwent risk-reducing BSO without hysterectomy found that although the overall risk of endometrial cancer after surgery did not appear to be increased, there was a small absolute increased risk of more aggressive serous histologic subtypes.[51] These are preliminary data, but some have interpreted this as a reason to consider total hysterectomy at the time of risk-reducing salpingo-oophorectomy, particularly in patients with *BRCA1* mutations, if there is not an otherwise compelling reason to leave the uterus intact.

There are no proven risk-reducing surgical options for male mutation carriers. Therefore, the following screening strategy is recommended for men with *BRCA* mutations: 1) monthly breast self-examination starting at age 35 years; 2) clinical breast examination every 12 months starting at age 35 years; 3) possible baseline mammogram at age 40 years; and 4) prostate cancer screening starting at age 40 years for *BRCA2* carriers.[14]

No consensus exists regarding screening for melanoma or pancreatic cancer, but possible suggestions have included full-body skin examinations and research trials for pancreatic cancer screening. The International Cancer of the Pancreas Screening Consortium recommends that persons with a *BRCA2* mutation who have at least one first-degree relative with pancreatic cancer undergo initial screening with endoscopic ultrasonography and/or magnetic resonance cholangiopancreatography.[27]

Looking Toward the Future

During the past 5 years, genetic testing for hereditary breast and ovarian cancer has become increasingly widespread in the United States. As a result, clinics have been established to provide

more personalized, specialized, and comprehensive care for patients who are carriers of specific genetic mutations. Currently, clinical trials are evaluating targeted therapy for mutation carriers with cancers related to their hereditary cancer risk. Relatively recent changes in access and technology have resulted in the expansion of access to genetic testing and a reduction in its cost. Thus, research regarding the cost-effectiveness of screening protocols, diagnostic techniques, and particularly treatments for persons with germline breast and ovarian cancer predisposition mutations is in its infancy, and data remain quite limited.

As with any genetic test, patients who are tested for hereditary breast and ovarian cancer should be educated about the test (ie, multiple genes, potential cancer associations, varied risk levels); the potential implications of all possible results (ie, positive, negative, and VUS); and appropriate long-term follow-up if results are positive (ie, medical management guidelines or lack thereof). Although ethical dilemmas are extremely rare, they may arise between clinicians and patients when there is a refusal to voluntarily disclose genetic results to potentially affected family members.[52] Clinicians sometimes have to consult medical geneticists, genetic counselors, lawyers, and/or bioethicists to help resolve the ethical conflict between the duty to protect patient privacy and autonomy and the duty to disclose for the purpose of preventing future harm to possibly affected family members. Patients often rely on clinician-provided educational resources to help facilitate discussions with family members. All patients who are found to be positive for an autosomal dominant gene, such as *BRCA1* or *BRCA2*, should be offered reproductive counseling and education about prenatal diagnosis and assisted reproduction.

Conclusions

In the new era of rapid, easy, and inexpensive next-generation sequencing, hereditary breast and ovarian cancer and its screening, diagnosis, and treatment have continued to garner nationwide attention. Medical societies are trying to come to a consensus regarding a practical clinical approach to handling all of the situations that may arise from genetic testing. As more complex genetic information becomes readily available, physicians and patients are faced with very difficult discussions about the meaning of genetic test results and how results influence the care of patients and their families.

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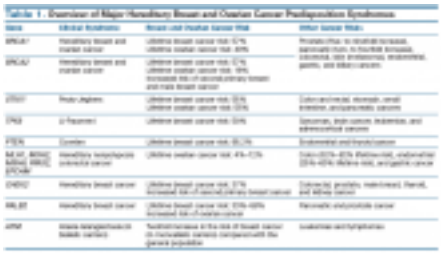

Table 1. Overview of Major Hereditary Breast and Ovarian Cancer Predis...

Table 2. Comparison of Commercially Available Genetic Tests for Heredi...

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