Personalized management of patients at risk ideally should involve a multidisciplinary team of not only genetic counselors and surgeons, but also women’s health or menopause specialists, knowledgeable psychologists, and primary care providers or obstetrician-gynecologists aware of the risks and fears “previvors” (survivors of a predisposition to cancer who have not had the disease) face as well as the issues that are common postoperatively. Identification of patients at risk for hereditary cancer, understanding of current genetic testing modalities and potential results, knowledge about screening and prevention including timing of surveillance, preventive medication and risk-reducing surgeries, understanding limitations and comorbidities associated with these risk management strategies and long-term psychological support are all important in hereditary cancer management. We describe issues surrounding the identification of the high-risk patient, universal testing in breast and ovarian cancer, and testing in special populations. We describe a simplified approach to understanding and communicating genetic testing results and nuances of testing including direct-to-consumer testing. We highlight concerns surrounding breast cancer screening during pregnancy and lactation. A framework for practical management and counseling of women who opt for risk-reducing salpingo-oophorectomy or risk-reducing mastectomy or both is provided. We provide an in-depth discussion of questions that arise in relation to timing of surgery, fertility preservation, management of menopausal symptoms, and surgical technique. Alternative choices in women who choose to delay bilateral salpingo-oophorectomy are reviewed. Finally, the psychosocial effects of carrying a genetic mutation and the issues that women face when undergoing to risk-reducing surgery including adjustment, sexuality issues, and cosmesis are addressed.

Testing for hereditary predisposition to breast and ovarian cancer is rapidly expanding, given the significant implications for screening, risk reduction, and cancer therapeutics for women with identified gene mutations, as well as increased awareness, decreased cost, and consumer-driven testing options.

With multiple genes being tested and myriad possible results and consequences for patients and their families, it is critical to promote understanding by both patients and health care professionals of risks, timing, and options for risk management. Guidelines exist to facilitate a multidisciplinary approach to management of individuals identified as being at increased risk, but caring for individual patients is nuanced and there are many areas of controversy. The focus of this review is “previvors,” survivors of a predisposition to cancer but who have not had the disease.

CONTROVERSIES IN GENETIC COUNSELING AND TESTING

Hereditary cancers are characterized by germline mutations associated with increased risk for certain cancers and transmission to offspring through either the maternal or paternal lineage. Individuals from...
these families often have an early age of onset of cancer and families exhibit an autosomal dominant pattern of inheritance. Early identification of families at risk may inform recommendations for earlier and more comprehensive screening and risk-reducing interventions and may even have important treatment implications for patients diagnosed with breast or ovarian cancer.

There are subtleties that accompany genetic testing and interpretation of results that are important for the obstetrician–gynecologist (ob-gyn) and other women’s health care professionals to recognize. It is also important to perform risk estimation in unaffected individuals with significant family history who have negative genetic test results to manage them appropriately. Given the advent of next-generation sequencing technology, which provides the ability to sequence multiple genes simultaneously at lower cost, and the genetic heterogeneity of breast and ovarian cancer susceptibility, multitarget panel testing has become commonplace.

Who Should Be Referred for Genetic Testing?
Health care professionals seeing patients in general practice often need to make decisions about referral to genetic counseling for their patients. The American College of Obstetricians and Gynecologists recommends that ob-gyns obtain a thorough personal and family history and assessment of other cancer risk factors, updated regularly. The U.S. Preventive Services Task Force recommends that women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility gene mutations (BRCA1/2) undergo genetic counseling, and, if indicated after counseling, genetic testing. The National Comprehensive Cancer Network has expanded testing criteria for high-penetration breast cancer or ovarian cancer susceptibility genes, or both, including BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53, among others that have been found to be associated with hereditary risk. General recommendations for testing are highlighted in Box 1.

Multiple national organizations have published guidelines to aid health care professionals in identifying individuals at greatest risk for carrying a pathogenic variant in a breast cancer susceptibility gene. Pathogenic variants in breast cancer susceptibility genes tend to result in earlier age at diagnosis (45 or younger to 50 years); multiple breast cancers in the patient or their family; and an increased risk for phenotype-related cancers (eg, ovarian, pancreatic, and prostate). Additionally, pathology (triple-negative breast cancer), ethnic background (Ashkenazi Jewish ancestry), and associated benign clinical features (eg, macrocephaly, Lhermitte-Duclos disease, and trichilemmomas with PTEN) may also inform genetic testing.

Women with Ashkenazi ancestry are 10 times more likely to have a BRCA1 or BRCA2 mutation than women in the general population, with 1 in 40 carrying a mutation in these genes. Consideration is now given to BRCA4 testing in Ashkenazi individuals with no cancer family history. Individuals with either a known pathogenic variant in their family or a pathogenic variant identified in somatic tumor-based testing should also consider testing. Lastly, genetic testing for unaffected individuals with a family history of the

<table>
<thead>
<tr>
<th>Box 1. Who Needs Breast or Ovarian Cancer Genetic Testing? Rule of 1-2-3 for Hereditary Breast and Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. One of the below diagnoses in a patient or a 1st- or 2nd-degree* relative:</td>
</tr>
<tr>
<td>• Breast cancer before 50 y of age</td>
</tr>
<tr>
<td>• Ovarian cancer at any age</td>
</tr>
<tr>
<td>• Pancreatic cancer at any age</td>
</tr>
<tr>
<td>• Triple-negative breast cancer 60 y of age or younger</td>
</tr>
<tr>
<td>• Male breast cancer at any age</td>
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<tr>
<td>• Metastatic prostate cancer at any age; prostate cancer with intraductal–cribriform histology</td>
</tr>
<tr>
<td>• Ashkenazi descent with breast, ovarian, pancreatic, or intraductal prostate cancers at any age</td>
</tr>
<tr>
<td>• Family history of a known member with a mutation for a breast cancer susceptibility gene</td>
</tr>
<tr>
<td>• A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline</td>
</tr>
<tr>
<td>2. Two cancer diagnoses in a patient or family member(s):</td>
</tr>
<tr>
<td>• Two primary breast cancers in the same individual, with the first before 50 y of age</td>
</tr>
<tr>
<td>• Two relatives (1st-, 2nd-, or 3rd-degree, on the same side of the family) diagnosed with breast cancer, one before 50 y of age</td>
</tr>
<tr>
<td>3. Three breast cancers in the patient or close blood relatives or both</td>
</tr>
</tbody>
</table>

Data from the National Comprehensive Cancer Network, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force. *First-degree relatives include parents, siblings, and children. Second-degree relatives include half-siblings, grandparents, aunts, uncles, nieces, nephews, and grandchildren. Close blood relatives include first-, second-, or third-degree relatives on either the maternal or paternal side of the family. Consider testing in the following scenarios: 1) bilateral breast cancer first diagnosed between the ages of 50 and 65 years, 2) an unaffected Ashkenazi Jewish individual.
mentioned red flags would also be appropriate for testing, if not possible in the affected family member.\textsuperscript{16,17} It is important to note that until 2013, only single syndrome testing was available, addressing the most likely genes responsible for the cancers seen in a family. Therefore, patients who had single gene testing before the fall of 2013 might consider returning for multi-gene panel testing.

**Universal Testing in Breast Cancer**

Areas of controversy regarding genetic testing include consideration of the testing of all patients with breast cancer, and universal testing of all women by the age of 30 years due to concern that existing guidelines may miss a significant number of patients with a hereditary cancer syndrome. For example, Beitsch et al reported a mutation rate of 7.9\% in patients with breast cancer who did not meet 2.2017 National Comprehensive Cancer Network criteria for genetic testing compared with a mutation rate of 9.3\% in those who did meet criteria in a total of 959 patients with breast cancer \( P\lt 0.025 \).\textsuperscript{9} Based partly on this research, in February of 2019, the American Society of Breast Surgeons issued a new genetic testing guideline stating, "genetic testing should be made available to all patients with a personal history of breast cancer."\textsuperscript{10} However, critics of this guideline have called into question its practicality and its extent of application. Specific concerns include debate over which genes should be tested, whether patients would receive adequate pretest and posttest genetic counseling, and how the test will be paid for. Dr. Mary-Claire King, credited with the discovery of the \textit{BRCA1} gene in 1994, on winning the national Lasker Award for Science in 2014, suggested that all women have \textit{BRCA} testing by the age of 30 years regardless of race or ethnicity.\textsuperscript{11} To date, these guidelines have not been broadly incorporated as standard of care. Third-party payer reimbursement is largely governed by eligibility for testing per National Comprehensive Cancer Network guidelines in conjunction with formal genetic counseling; many patients, however, are opting for affordable clinical grade options now available for personal use (also in conjunction with genetic counseling). However, the overall debate of guidelines-based testing compared with a more generalized testing approach continues.

**Universal Testing in Ovarian Cancer**

Although it was previously believed that about 10\% of ovarian cancers are caused by inherited mutations, it was recently determined that the incidence of germline mutations in \textit{BRCA1} and \textit{BRCA2} genes among women with invasive epithelial ovarian cancer is up to 20\%,\textsuperscript{12–14} When other mutations within the homologous recombination–Fanconi anemia DNA repair pathway are taken into consideration, such as \textit{PALB2}, \textit{BRIP1}, \textit{BARD1}, \textit{RAD51C}, and \textit{RAD51D}, the incidence of germline mutations among unselected patients with ovarian cancer is increased further to up to 25\%, with 18\% of mutations attributed to \textit{BRCA1} and \textit{BRCA2} genes.\textsuperscript{12,13} Norquist et al reported on 1,915 patients with ovarian cancer who underwent multigene panel testing and 18\% carried pathogenic germline mutations; \textit{PALB2} and \textit{BARD1} were suspected and, together with \textit{BRCA1}, \textit{BRCA2}, \textit{BRIP1}, \textit{RAD51C}, \textit{RAD51D}, \textit{MLH1}, \textit{MSH2}, \textit{PMS2}, and \textit{MSH6}, bring the total number of genes suspected to cause hereditary ovarian cancer to 11.\textsuperscript{12} Furthermore, a significant family history is absent in 27–56\% of women with germline \textit{BRCA1/2} mutations, and it is now recognized that family history along with age and race are poor predictors of mutation frequency.\textsuperscript{15} Although the mutation frequency is known to be highest among women with high-grade serous ovarian cancer, recent data have shown that the mutation frequency for women with tumors of other histology is also significant.\textsuperscript{12} Women with clear cell and low-grade serous ovarian cancer have an 8\% and 6\% risk, respectively, of having a genetic mutation. As such, the Society of Gynecologic Oncology and the National Comprehensive Cancer Network have endorsed genetic testing for all women diagnosed with epithelial ovarian cancer regardless of histology.\textsuperscript{16} Given that up to a quarter of women with epithelial ovarian cancer may carry a germline genetic mutation, and mutations in homologous repair deficiency genes are highly predictive of response to novel targeted therapy with polypt ADP-ribose polymerase inhibitors, it is crucial that all women with a diagnosis of epithelial ovarian cancer be referred for genetic counseling and testing shortly after diagnosis. Somatic tumor testing is recommended if germline DNA sequencing is negative, as an additional 5\% of women will have a somatic mutation in \textit{BRCA4} or related genes.\textsuperscript{17} Although mucinous epithelial ovarian cancer is not associated with \textit{BRCA1/BRCA2} and related gene mutations, it can be associated with p53, KRAS mutations or mismatch repair deficiency (in up to 20\%).\textsuperscript{17} Therefore multigene panel testing may be of value even among patients with mucinous ovarian carcinoma.\textsuperscript{6}
syndrome is prevalent in approximately 2–5% of women diagnosed with endometrial cancer and is caused by germline mutations in one of the four DNA mismatch repair genes: MLH1, MSH2, MSH6, and PMS2 or the EPCAM gene. Women with Lynch syndrome have a 16–70% lifetime risk of developing endometrial cancer compared with 2–3% in the general population, and a 25–61% lifetime risk of developing colon cancer. The risk of ovarian cancer is approximately 11–38% for women with MLH1 and MSH2 mutations. Clinical screening based on a focused personal and family history has been shown to miss a significant number of women with Lynch syndrome. Molecular tumor testing using immunohistochemistry for the four mismatch repair genes or microsatellite instability analysis and MLH1 methylation testing has been identified as a cost-effective strategy and can direct targeted germline genetic testing. It is noteworthy that approximately 25% of endometrial cancers that demonstrate loss of MLH1 are due to MLH1 hypermethylation, which is a sporadic cause of endometrial cancer. It is currently recommended that molecular testing be performed on pathology tissue in patients diagnosed with endometrial and colon cancer regardless of age whenever resources for testing are available.

**Understanding Genetic Testing Results**

**Counseling, Consent for Testing, and Cost Considerations**

Ensuring informed consent and patient comprehension of potential results is critical in the genetic testing process. Patients are encouraged to first pursue pretest genetic counseling with either a licensed genetic counselor or another genetics professional. Otherwise, many insurance companies will not pay for testing. Through genetic counseling, family history is expanded, and the potential is discussed to reveal effect beyond common cancers, effect to family members, incidental findings, and findings of uncertain clinical significance. Cost, insurance coverage, and laws protecting individuals from job or health care discrimination based on genetic information are discussed.

If there is a known pathogenic variant in the family, patients understand that they will have a true-positive or true-negative test result. With highly penetrant genes, those with true-negative results return to population risk, whereas, with moderate-risk genes, those with true-negative results are still presumed to be at increased risk due to the potential of shared environmental exposures and the possible contribution of other factors not related to the identified moderate-risk gene. Patients must understand the meaning of uninformative negative results and variants of uncertain significance.

**Variants of Unknown Significance**

Counseling is vital to ensure patient comprehension and ease in the delivery of results. Specific examples underscore the value of pretest counseling. Broad pan-cancer gene panels can reveal mutations in common genes such as monoallelic MUYTH or APC/1307K (the latter being seen in 10% of individuals in the Ashkenazi community), which are felt to be unrelated to breast cancer; conversely, finding a true germline mutation in TP53 revealing significant cancer risks has profound effect on the patient and also on their children and relatives. Mutations in CDH1 revealing potentially very high gastric cancer risks (particularly in a family with no prior gastric cancer history) lead to very challenging discussions around the possibility of risk-reducing gastrectomy. Finally, with panel testing, variants of uncertain significance are common, occurring approximately 25% of the time. A variant of uncertain significance indicates that a gene mutation has been identified that has an unknown effect on protein function and an uncertain association with cancer risk. Variants of uncertain significance can also be a source of uncertainty for providers and may lead to overtreatment, excessive surveillance, and unnecessary preventive measures.

**Disclosure and Discussion of Genetic Testing Results**

Numerous guidelines and professional societies indicate that pretest and posttest genetic counseling is best completed by a specialist in cancer genetics or a health care professional with expertise in genetics. The results disclosure conversation includes the effect of the findings on the patient and their family, risk management options, and provision of available resources. Discussion of management should outline recommendations related to multidisciplinary care if other organs are at risk. Because mutations associated with hereditary breast and ovarian cancer are inherited in an autosomal-dominant fashion, parents, siblings, and children of a person carrying a mutation have a 50% chance of having that mutation. Extended family members may also be at increased risk. Identifying at-risk family members and discussing strategies for the patient to notify them is essential. Caution should be given to interpretation of variants of uncertain significance and uninformative negative results. In both scenarios, a patient’s personal and family history, not their genetic test result, should be used to determine medical management recommendations.
Direct-to-Consumer Genetic Testing

Direct-to-consumer genetic testing has added a layer of additional challenge. Clinicians must understand the different tests, their strengths and limitations, and recognize the key differences in the types of testing to apply this to clinical practice and to provide proper patient education surrounding this topic. There are significant limitations of common “recreational” testing and potential false reassurance with negative results. Furthermore, “positive” results are often inaccurate and require verification in a clinical laboratory. Most recreational testing uses a form of microarray-based genotyping of predefined single nucleotide polymorphisms (SNPs) for their assay. Clinical grade next-generation sequencing, which is the standard of care method for diagnosis of genetic mutations, is generally not performed through most commercial assays. Third-party interpretation services are available to further evaluate the “data” derived from the commercial SNP-based products. They operate by querying different publicly available SNP databases with reported disease associations in the medical literature that may be inaccurate. In one study of these data, 40% of the reported actionable variants were actually false-positive results. Clinical grade, next-generation multi-gene testing, however, is also now available in a consumer-directed form, in conjunction with genetic counseling services. Abnormal results, or pathogenic or likely pathogenic variants, identify a clear and accurate increased risk of disease based on the mutation involved, and do not require confirmation.

SCREENING AND PREVENTION

For unaffected patients with pathogenic variants in high-risk genes, general management consists of enhanced surveillance, preventive medications, and consideration of risk-reducing surgeries (breast and ovary). Table 1 summarizes the genes for which consideration of MRI screening for breast cancer is recommended, the genes for which a discussion around risk-reducing mastectomy is undertaken, the genes for which salpingo-oophorectomy is recommended, and the genes for which pancreatic cancer screening might be considered. These recommendations are based on estimations of penetrance, age at onset of disease, and sensitivity of screening. In patients who are undergoing active treatment for metastatic breast or ovarian cancer, decisions about screening should be made at discretion of the practitioner, and shared decision making is encouraged in coordination with the patients’ oncologist.

Ovarian Cancer Screening

The cumulative lifetime risk of ovarian cancer by age 80 years is 44% for women with BRCA1 mutations and 17% for those with BRCA2 mutations based on a prospective cohort study of almost 10,000 patients. Tailored screening and prevention strategies have been shown to detect the majority of cancers early and significantly reduce overall morbidity associated with breast cancer. Ovarian cancer screening, however, is controversial and, in the general low-risk population, has not been shown to provide a significant mortality benefit. Ovarian cancer screening in high-risk women remains a controversial area. In women with gene mutations at risk for ovarian, fallopian tube, and primary peritoneal cancers, targeted multimodal screening using an ultrasonography- and CA 125–based model has been shown to be potentially promising, with more women being diagnosed at an earlier stage with lower-volume disease based on large, population-based studies. However, the effect of such screening modalities on survival remains unknown. At this time, risk-reducing surgery is the standard of care for management of high-risk women who carry genetic mutations. Women at risk can be offered screening with transvaginal ultrasonography and serum CA 125 starting at the age of 30–35 years at the discretion of their managing physician.

Management of Women With Moderate Ovarian Cancer Penetrance Genes

Women who carry a mutation in BRIP1, PALB2, BARD1, RAD51C, or RAD51D have an estimated lifetime risk of ovarian cancer of approximately 5–15%, which is lower than that seen in women with BRCA1 or BRCA2 mutations. Case-control studies in women with epithelial ovarian cancer have shown that RAD51C and RAD51D are associated with a significantly increased risk for ovarian cancer (odds ratio 5.2 95% CI 1.1–24 for RAD51C and odds ratio 12; 95% CI 1.5–90 for RAD51D, respectively). Patients who carry mutations in these low penetrance genes also appear to be diagnosed at a later age (around 50–55 years). Because many of these women may have additional risk factors for ovarian cancer (eg, family members, nulliparity), delaying risk-reducing surgery may miss the opportunity to prevent ovarian cancer. Therefore, the National Comprehensive Cancer Network currently recommends consideration of risk-reducing salpingo-oophorectomy in women with BRIP1, RAD51C, and RAD51D beginning at age 45–50 years.
Management of Women With Lower (Ovarian Cancer) Penetrance Genes

The genetic testing landscape is rapidly changing with the introduction of complex multigene panel testing that assess cancer risk through testing for a number of cancer susceptibility genes for less common or lower penetrance genes. For example, germline mutations in the genes DICER1 and STK11 (Peutz Jeghers syndrome) have been shown to be associated with Sertoli Leydig cell tumors of the ovary and SMARC1 is associated with small cell ovarian carcinoma. Patients with Peutz Jeghers syndrome should have annual pelvic examinations with PAP tests from the age of 18 years. There are no formal guidelines currently for patients with DICER1 or SMARC1. Risk-reducing surgery can be considered based on family history but is not required as part of risk-reducing strategies for Peutz Jeghers syndrome. The National Comprehensive Cancer Network recommends referral of these patients to a specialized team for risk management and education on symptoms that might be associated with development of ovarian cancer and other gynecologic cancers.

Management of Women With Lynch Syndrome

Genetic mutations in the mismatch repair genes MSH2, MSH6, MLH1 carry an increased risk of ovarian cancer (10–25%) associated with Lynch syndrome (insufficient evidence for PMS2-associated ovarian cancer risk) and an increased risk of synchronous endometrial and ovarian carcinoma. Because there is no effective screening for ovarian cancer, women should be educated on symptoms that might be associated with the development of ovarian cancer and that risk-reducing bilateral salpingo-oophorectomy may reduce the incidence of ovarian cancer. Hysterectomy with bilateral salpingo-oophorectomy is recommended for patients with Lynch syndrome. The timing of risk-reducing surgery in patients with Lynch syndrome is individualized based on whether childbearing is complete, comorbidities, menopausal status and Lynch syndrome pathogenic variant, as risks for endometrial and ovarian cancer vary by gene.

Women with Lynch syndrome have a 16–70% lifetime risk of endometrial cancer. Surveillance and prevention of endometrial cancer in women with a diagnosis of Lynch syndrome consists of annual gynecologic examinations and education on symptoms, specifically abnormal uterine bleeding or postmenopausal bleeding that would prompt evaluation with endometrial biopsy. Although there is no strong evidence regarding endometrial cancer screening in this population, National Comprehensive Cancer Network guidelines recommend consideration of endometrial biopsy every 1–2 years starting at age 30–35 years given the high sensitivity and specificity of diagnostic endometrial biopsies. Transvaginal ultrasonography is not recommended as an endometrial cancer-screening tool in premenopausal women with Lynch syndrome due to variation in endometrial thickness with menstrual cycle. Hysterectomy eliminates the incidence of endometrial cancer in this patient population.

Breast Cancer Screening

Management of Women With High-Risk and Moderate-Risk Genes

Breast screening of women with highly penetrant gene mutations (BRCA1, BRCA2, PALB2, CDH1, PTEN, and TP53) is largely guideline driven. Given clear
estimations of penetrance, recommendations and age at which screening should commence are provided by the National Comprehensive Cancer Network based on large bodies of evidence. Management of women with pathogenic variants in moderate-risk genes presents unique challenges. Unlike highly penetrant genes where a woman is more likely than not to be diagnosed with breast cancer in her lifetime, carrying a genetic mutation in the common genes ATM and CHEK2 can be viewed to an extent as a significant risk factor for the development of breast cancer similar to that conferred by a benign atypical biopsy. The lifetime risk for breast cancer with ATM and CHEK2 mutations is approximately 30%. Breast screening consists of an annual mammogram (with consideration of tomosynthesis) and consideration of breast MRI beginning at age 40 years. These recommendations may be modified based on family history (screening may begin typically 5–10 years earlier than the first affected relative). Breast cancer screening and risk reducing surgery in women with a diagnosis of ovarian cancer is discussed in Appendix 1, available online at http://links.lww.com/AOG/C275.

Breast Cancer Screening During Pregnancy and Lactation

National Comprehensive Cancer Network guidelines state that mammography of the breast with shielding can be done safely in pregnant women (Appendix 1, available online at http://links.lww.com/AOG/C275). The fetal radiation dose from a four-view mammogram is less than 0.03 mGy. No teratogenic effects have been demonstrated below 50 mGy. Screening mammography (including digital breast tomosynthesis), can be considered in women at increased risk during pregnancy or at least immediately postpartum. The American College of Radiology (ACR) does not recommend intravenous administration of gadolinium during pregnancy. The American College of Obstetricians and Gynecologists does not recommend interruption of breastfeeding after gadolinium administration. During lactation, screening MRI is not contraindicated but sensitivity is limited by increased background enhancement. A woman should breastfeed or pump immediately before a mammogram or MRI in an effort to reduce mammographic density and background enhancement on MRI. If a woman plans to breastfeed longer than 6 months, a screening MRI is a reasonable option during this time period. If a woman is going to breastfeed for less than 6 months, it is reasonable to wait 6–8 weeks after she stops to resume screening, preferably 7–15 days after the resumption of her first menstrual period.

Chemoprevention

Another pillar of risk management is chemoprevention. The use of estrogen receptor agonist–antagonists (ERAs) (tamoxifen and raloxifene, also known as selective estrogen receptor modulators or SERMs) and aromatase inhibitors (anastrozole and exemestane) has been shown to reduce the risk of invasive breast cancer in women at risk, but data are extremely limited in those with genetic mutations. As these medications reduce the risk of estrogen receptor (ER)–positive cancers, it is not surprising that, in the Breast Cancer Prevention Trial, breast cancer risk was reduced by 62% in those with a BRCA2 mutation but there was no reduction in risk in those with a BRCA1 mutation (who are prone to ER-negative disease).

CONSIDERATIONS FOR RISK-REDUCING SURGERY

Age-Specific Recommendations for Risk-Reducing Salpingo-Oophorectomy

Counseling women on age-specific and cumulative risk of ovarian cancer can assist with decision making. Up to 20% of women with the BRCA1 mutation develop ovarian cancer by the age of 50 years compared with 3% of those with the BRCA2 mutation. As such, it is recommended that women who carry the BRCA1 mutation undergo risk-reducing surgery between age 35 and 40 years, whereas those with BRCA2 mutations may undergo surgery between age 40 and 45 years, because the age of onset of ovarian cancer in women with BRCA2 mutations is, on average, 8–10 years later than in those with BRCA1 mutations. These recommendations are supported by the National Comprehensive Cancer Network. Women who undergo risk-reducing surgery at the recommended age have a significantly reduced overall mortality rate and reduced risks of breast and ovarian cancer. Risk-reducing bilateral salpingo-oophorectomy reduces the incidence of ovarian cancer up to 96% and breast cancer up to 50%. Breast cancer-specific mortality is significantly reduced in women with BRCA mutations (hazard ratio 0.45).

Timing of Risk-Reducing Salpingo-Oophorectomy

Fertility Considerations

There are currently no conclusive data to suggest that women who carry a genetic mutation in BRCA1 or BRCA2 are at increased risk for premature menopause or infertility. Fertility preservation is an important consideration in women with genetic mutations, because these women generally are faced with the
decision to consider risk-reducing surgery during childbearing years (ages 35–45 years). As such, early referral to a reproductive endocrinology specialist is advised (consider a conversation by age 30 years). With the growth of fertility treatment options for women who chose to delay childbearing, these women have the option of oocyte or embryo cryopreservation and in vitro fertilization (IVF) to maximize the chances of carrying a biological child. Comprehensive discussion about the risks, benefits, and limitations associated with reproductive technology options are best done by a reproductive endocrinology specialist. Awareness about the potential number of cycles that may be feasible and needed for adequate oocyte harvesting, success rate of the clinic, the influence of age and comorbidities on success of IVF are important components of patient counseling. In addition, women with mutation are offered evaluation to determine baseline ovarian reserve through testing of antimüllerian hormone levels, day 3 follicle-stimulating hormone with estradiol levels, or transvaginal ultrasonography measurement of antral follicle count. This helps inform decisions on timing of fertility preservation and may facilitate decision making.

Concerns regarding the risk of breast cancer, ovarian cancer, or uterine cancer with artificial reproduction technology are often raised. Women should be counseled that there is currently no evidence that fertility medications increase the risk of breast cancer or ovarian cancer. In addition, women who undergo IVF are candidates for the gonadotropin plus letrozole stimulation protocol, which does not increase estradiol levels above physiologic levels and has been deemed to be safe among patients with a history of breast cancer based on available data. Many women may not be able to consider artificial reproductive technology due to financial, ethical, or religious considerations. Providing patients with adequate resources to make these decisions and individualized counseling is imperative in this regard.

Preimplantation Genetic Diagnosis
Apart from discussion of fertility preservation options, women should be counseled about the option of preimplantation genetic diagnosis to minimize transmission of the genetic mutation to the fetus. This process allows the selection of unaffected embryos that have been genetically tested to be transferred after IVF. In a study of BRCA1-positive unaffected women and those with breast cancer who underwent preimplantation genetic diagnosis, the rate of detection of BRCA-negative embryos was 41%. Data on the success of preimplantation genetic diagnosis in combination with artificial reproduction technology in women with BRCA1 and BRCA2 mutations are limited, and long-term data are not available. However, data from patient surveys administered to those at high risk for breast or ovarian cancer suggest that the vast majority of patients have little or no knowledge about preimplantation genetic diagnosis. These surveys also indicate that 14–33% of patients would consider undergoing preimplantation genetic diagnosis. Increasing awareness about the availability of preimplantation genetic diagnosis and its utility is important in the comprehensive care of young women with hereditary breast and ovarian cancer. Cost is significant and typically not covered by insurance. Psychological evaluation and support around this decision and process is also advisable if available.

Salpingectomy and Delayed Oophorectomy
Delayed oophorectomy has been proposed to avoid surgical menopause and allow for fertility preservation with retention of endogenous hormone production. The practice of performing risk-reducing salpingectomy before oophorectomy evolved from evidence that high-grade serous cancers primarily originate in the fallopian tube. Some retrospective studies in low-risk women have suggested a 35–42% reduction in risk of ovarian cancer after salpingectomy. However, there are no data on actual risk reduction achieved after bilateral salpingectomy alone in high-risk patients, and therefore, to date there is insufficient evidence to recommend salpingectomy for the purpose of risk reduction. Although this practice may reduce anxiety and worry among women with gene mutations, the effect on ovarian cancer mortality is not known. Therefore, women who decline risk-reducing bilateral salpingo-oophorectomy in favor of bilateral salpingectomy should be informed that the oncologic safety of this procedure has not been determined, and reduction in breast cancer risk cannot be gleaned by performing salpingectomy alone. Currently, women have been offered interval salpingectomy and delayed oophorectomy as part of a clinical trial and these women are still recommended to undergo screening until definitive oophorectomy is performed.

There are two ongoing prospective observational clinical trials evaluating women at high risk for ovarian cancer who may opt for standard of care compared with risk-reducing salpingo-oophorectomy or interval salpingectomy with delayed oophorectomy, the TUBA study (Early salpingectomy [Tubectomy] with delayed oophorectomy to improve quality...
of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers) and the WISP study (Women Choosing Surgical Prevention).53,55 Preliminary data from the TUBA multicenter Dutch trial showed that cancer worry was improved in both the risk-reducing salpingo-oophorectomy and interval salpingectomy groups, and risk-reducing surgery was associated with low rates of regret. In the WISP study, preliminary results showed that women who underwent interval salpingectomy and those who chose risk-reducing salpingo-oophorectomy had significant improvement in cancer-related distress.56 However, providers must maintain caution in interpreting these results and advising patients due to lack of oncologic safety data.

**Contraception Choices and Safety in Women Who Delay BSO**

Oral contraceptive pills (OCPs) are associated with reduction in risk of ovarian cancer by 50% in average risk women as well as women who carry a genetic mutation in BRCA1 or BRCA2.45 This benefit increases with duration of use. Cohort studies have demonstrated a potential increase in breast cancer risk; however, the largest meta-analysis to date demonstrated no increase in risk compared with the general population.57,58 In a large meta-analysis of 18 comparative retrospective studies of OCP use in women with BRCA1 and BRCA2 mutations, there was no evidence of an increased risk of breast cancer with the use of current formulations of OCPs or in the first 10 years after cessation of OCP use.59 There are no current formal recommendations for or against the use of OCPs for primary prevention of ovarian cancer, as there have been case control studies showing increased risk for the development of breast cancer.60,61 Larger prospective trials are needed to elucidate the effect of oral contraceptives on cancer risk in women with BRCA mutations.

Despite the ongoing controversy and emergence of studies showing potential increases in risk of breast cancer with hormonal contraception use, including levonorgestrel intrauterine devices,62,63 it is important that patients are well-informed that their overall cancer risk is reduced with the use of hormonal contraception (particularly ovarian cancer and endometrial cancer) and that their absolute breast cancer risk at the age at which they are using hormonal contraception is very low. The increased risk of breast cancer among hormonal contraceptive users (in the general population) is comparable with one additional case of breast cancer for every approximately 7,500 users of hormonal contraception.57 The contraceptive and health benefits must be closely weighed with the potential risks when counseling patients. These patients should be informed about the option of nonhormonal contraception, such as the copper intrauterine device.

**Technical Considerations for Risk-Reducing Salpingo-Oophorectomy**

Per National Comprehensive Cancer Network and American College of Obstetricians and Gynecologists guidelines, a systematic approach is generally undertaken where abdominal survey is performed and all peritoneal surfaces are closely inspected.6 Obtaining peritoneal washings is an important component of risk-reducing surgery.64 The retroperitoneal space is entered, the ovarian vessels are ligated at the pelvic brim (at least 2 cm), and the fallopian tube and ovary are removed in their entirety. It is important to remove the fallopian tubes at their insertion point due to the risk of interstitial fallopian tube carcinoma.65 After surgery, pathologic evaluation with sectioning and extensive examination of the fimbriated end of the fallopian tube is performed with 2–3 mm fine sections examined. Longitudinal sections are obtained for analysis and specimen labeling with diagnosis such as BRCA must be used.66 This process allows for an increased detection rate of occult carcinoma by 40–60%,67,68 If carcinoma is detected postoperatively, the patient may need to be taken back for surgical exploration and staging. The incidence of visually detected carcinoma at the time of risk-reducing surgery requiring conversion to a staging procedure is approximately 1% based on a recent study of 269 patients undergoing risk-reducing procedures over a 20-year period at a large academic institution.69

**Role of Gynecologic Oncologists in Screening and Performing Risk-Reducing Procedures**

In view of the complexity associated with counseling regarding cancer risk, decision making and the risk of occult malignancy detection at the time of risk-reducing surgery, early consultation with a genetic counselor as well as a gynecologic oncologist is recommended.16 The effect of performing risk-reducing surgery in women of reproductive age and long-term risks of premature menopause (eg, osteoporosis, cardiovascular disease and sexual concerns) must be addressed. In general, the risk of detecting an occult malignancy at the time of risk-reducing bilateral salpingo-oophorectomy is approximately 3–4% (4.5% for women with BRCA1 mutations and 3.5% for those with BRCA2 mutations).52,70 However, estimates of up to 10% of occult cancer have been described with rigorous pathologic examination of
the ovaries and fallopian tubes.\textsuperscript{71} This risk has been shown to vary with age and patient population studied. Preoperative evaluation with transvaginal ultrasonography and CA 125 is warranted before risk-reducing bilateral salpingo-oophorectomy. Surgical technique has been suggested to account for the variation in the rate of detection of occult malignancy at the time of risk-reducing surgery. Data have consistently shown higher adherence rate with recommended practices for risk-reducing surgery when patients are followed by gynecologic oncologists in addition to higher rates of diagnosis of occult neoplasms.\textsuperscript{60,69} Therefore, referral to gynecologic oncology is highly recommended.

Role of Concurrent Hysterectomy

Women should be counseled about the risks and benefits of undergoing concurrent hysterectomy at the time of risk-reducing surgery. At present, about 50\% of women with \textit{BRCA} mutations elect to undergo concurrent hysterectomy based on survey studies, and approximately 40\% of providers recommend hysterectomy.\textsuperscript{72} Although women planning to take tamoxifen and those with a known diagnosis of Lynch syndrome are most likely to benefit from additional risk reduction with hysterectomy,\textsuperscript{56} the benefits must be weighed against the potential surgical risks of adding hysterectomy, which have been described to be approximately 2–3\%.\textsuperscript{73} Counseling regarding postmenopausal hormone therapy (HT) plays a role in decision making regarding hysterectomy, because estrogen alone is associated with a lower risk of breast cancer than combined estrogen and progesterone.\textsuperscript{74} Additionally, a possible association between serous uterine carcinoma and \textit{BRCA1} has been described. In a multicenter prospective cohort study of 627 women with \textit{BRCA1} mutations who underwent risk-reducing bilateral salpingo-oophorectomy with uterine conservation, an increased risk of serous endometrial carcinoma and serous-like cancer was reported (2.6–4.7\% risk up to age 70 years, with an observed/expected ratio of 22.1).\textsuperscript{75,76} This risk traditionally has been attributed to the use of tamoxifen in women with genetic mutations. National Comprehensive Cancer Network guidelines recommend individualized counseling and shared decision making regarding the potential increased risk of uterine serous carcinoma in women with \textit{BRCA1} mutations\textsuperscript{56} and the potential increase in breast cancer risk in young previvors who will embark on combined HT. Finally, limited evidence suggests that hysterectomy at the time of risk-reducing surgery may be more cost effective. This was based on a modified Markov decision model study that showed that the addition of hysterectomy to risk-reducing bilateral salpingo-oophorectomy is associated with lower cost and incremental cost-effectiveness ratio with age.\textsuperscript{60}

**Hormone Therapy After Risk-Reducing Salpingo-Oophorectomy**

**Oncologic Safety**

Approximately 65\% of women with \textit{BRCA1} mutations will undergo risk-reducing salpingo-oophorectomy before the age of natural menopause.\textsuperscript{77} After risk-reducing salpingo-oophorectomy, young women who encounter surgical menopause at are risk for symptoms that are likely to affect quality of life including vasomotor symptoms, sexual dysfunction, and cognitive changes. Hormone therapy has been shown to mitigate menopausal symptoms and improve quality of life, sexual function, and bone health. The risks of cardiovascular disease, early osteoporosis, and cognitive impairment are mitigated with HT.\textsuperscript{78} It has been shown that short-term HT in women who undergo risk-reducing salpingo-oophorectomy does not increase the risk of breast cancer, but long-term data are lacking.\textsuperscript{73} According to a longitudinal cohort study of 872 women with \textit{BRCA1} and \textit{BRCA2} mutations, the incidence of breast cancer was not increased after oophorectomy in women who received HT.\textsuperscript{77} An association between HT use in women with \textit{BRCA1} mutations and breast cancer risk in postmenopausal women has not been shown. However, in women who undergo early surgical menopause, \textit{BRCA1}-positive women who used estrogen alone had a 12\% cumulative incidence of breast cancer compared with 22\% among women who used both estrogen and progesterone.\textsuperscript{77} In the PROSE study (Prevention and Observation of Surgical Endpoints) study, which was a prospective cohort study that followed 462 women with \textit{BRCA} mutations for an average of 3.6 years, there was a significant reduction in risk of breast cancer associated with risk-reducing salpingo-oophorectomy and this risk reduction was not affected by the use of HT.\textsuperscript{73} The majority of these patients used estrogen alone. Therefore, in the setting of initiation of HT after risk-reducing salpingo-oophorectomy, use of estrogen alone is advised, which would entail hysterectomy at the time of risk-reducing surgery. Additional retrospective case control studies showed that HT use, duration, and formulation did not increase the risk of breast cancer.\textsuperscript{77,79}

It is important to acknowledge, however, that there are no randomized trials performed in this area (nor will there be), and the safety of HT in women who have undergone risk-reducing mastectomy is theoretically
justified. Shared-decision making is encouraged when counseling women about HT and discussion of non-hormonal options should be considered. These women are additionally counseled about the potential increase in risk of cardiovascular disease, osteoporosis, and all-cause mortality associated with premature menopause if HT is not given.\(^4^5\) Thus, the benefits of HT are likely to outweigh the risks in these situations and should be strongly considered in women without a history of breast cancer. To monitor compliance and long-term health of patients on HT after premature surgical menopause, it is important that these women are integrated into specialized clinics if available.

**Long-Term Health Consequences, Quality of Life, and Hormone Therapy After Risk-Reducing Surgery**

Women without a genetic mutation who undergo bilateral salpingo-oophorectomy before the age of 45 years and do not use HT have a markedly increased overall mortality (Appendix 1, available online at http://links.lww.com/AOG/C275).\(^8^0,8^1\)

Vasomotor symptoms (hot flushes) due to estrogen deprivation are associated with diminished quality of life and affect more than 80% of women undergoing risk-reducing surgery; 43–50% report decreased libido. In general, approximately 60% of women opt to use HT after risk-reducing surgery.\(^4^5,7^8\)

Women who have premature oophorectomy (before age 45 years) and do not take HT are noted have a twofold increased risk of death compared with women who did take HT. In a Markov decision analytic model that evaluated expected outcomes after risk-reducing bilateral salpingo-oophorectomy with or without HT (up to the age of 50 years or for life) in women with \(BRCA1/2\) mutations, risk-reducing surgery increased life expectancy. Hormone therapy was associated with a relatively small change in life expectancy when stopped at age 50 years. However, in this modeling study, extension of HT for life was associated with a reduced life expectancy.\(^7^2\) Women undergoing risk-reducing surgery should be reassured that menopausal symptoms, sexual function and quality of life can be improved with HT use and it is likely safe until the time of natural menopause (age 50–52).\(^7^6,8^3\)

**Considerations for Risk-Reducing Mastectomy**

Women with highly penetrant gene mutations often have many questions around risk-reducing mastectomy involving efficacy, timing, reconstructive options, risks and complications. It is a difficult, highly personal decision. A discussion around risk-reducing mastectomy is typically recommended for women with pathogenic variants in \(BRCA1, BRCA2, PTEN, TP53,\) and \(PALB2,\) but consideration can also be given to an unaffected woman with a compelling family history for breast cancer or possibly for women with prior thoracic therapeutic radiation before the age of 30 years.\(^8^4\) For some, it is a clear decision; others struggle with the pros and cons.

**Timing of Risk-Reducing Mastectomy**

Timing can be influenced by job restrictions, the wish to breastfeed, and the need to care for young children. It is important to emphasize to young women that their risk is low over the short-term. For example, the risk for a 25-year-old woman to get breast cancer before the age of 30 years is less than 5%. Conversely, a woman older than age 60 years with a \(BRCA2\) mutation has a reduced residual lifetime risk of less than 15%.\(^4^5\)

The timing of risk-reducing salpingo-oophorectomy in relation to risk-reducing mastectomy (with or without reconstruction) is controversial. Practice patterns generally vary by institution and health care professional. However, available evidence shows that combined procedures, particularly in high-volume institutions, are associated with reasonable postoperative outcomes without a significant increase in recovery time or cost.\(^8^0,8^3–8^7\)

**PSYCHOLOGICAL CONSIDERATIONS**

**Psychological Concerns in Women with Genetic Mutations**

Hereditary cancer risk produces feelings of fear and uncertainty. Health care professionals need to serve as informational sources, partners for decision making and providers of supportive communication. It is important to be aware of support networks for referral. Surveillance produces anxiety and distress in many individuals, particularly in those at risk for multiple cancers. Factors associated with worse psychological outcomes include a personal history of cancer, female gender, having a first-degree relative with cancer, negative illness perceptions, and coping style.\(^8^8\) Simple screening tools for anxiety and depression and the availability of psychological support provided by practitioners knowledgeable about hereditary cancer are critical in management. Health psychologists with expertise in caring for patients with hereditary cancer can be embedded into hereditary programs and are important members of the management team, when available.

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Learning Objectives for “Controversies in Hereditary Cancer Management”

After completing this learning exercise, the involved learner should be able to:

- Discuss the concept of “previvor”
- Identify patients at risk for hereditary cancer
- Understand current genetic testing modalities and potential results
- Demonstrate knowledge about screening and prevention, including timing of surveillance, preventive medication, and risk-reducing surgeries
- List limitations and comorbidities associated with these risk-management strategies
- Provide long-term psychological support to those women predisposed to inherited cancers

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