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Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes

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INTRODUCTION

Pathogenic (harmful) variants in the breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2* [*BRCA1/2*]) are very strong hereditary risk factors for the development of breast and ovarian cancer. Although most breast and ovarian cancers are sporadic, approximately 6 percent of breast cancer and 20 percent of ovarian cancer cases are caused by pathogenic variants in these genes [1-8]. Pathogenic variants in other high- to moderate-risk genes such as tumor protein p53 (*TP53*), partner and localizer of *BRCA2* (*PALB2*), phosphatase and tensin homolog (*PTEN*), checkpoint kinase 2 (*CHEK2*), and ataxia-telangiectasia mutated (*ATM*) account for a smaller percentage of breast, and, in some cases, ovarian, prostate, or pancreatic cancers [9-12].

As such, certain individuals with a personal or family history of breast, ovarian, prostate, or pancreatic cancer may benefit from hereditary risk evaluation to determine their own and family members' risk for these and associated cancers. For patients who undergo genetic testing, expertise is required to ensure that the appropriate testing is ordered, that it will be adequately interpreted, and that the results are likely to influence management of the patient or family members at risk for hereditary cancer [13]. The complexity involved in pre- and post-test risk assessment underscores the importance of genetic counseling both before and after testing.

This topic reviews the genetic testing and the interpretation of genetic tests that can identify individuals at high risk for what has been called hereditary breast and ovarian cancer

syndrome (HBOC). However, with the recognition that pathogenic variants in the most commonly implicated genes (*BRCA1/2*) also predispose to cancers affecting men, namely prostate and pancreatic cancer, the acronym HBOC is less inclusive [14].

The management of *BRCA1/2* carriers, and carriers of other pathogenic variants associated with breast, ovarian, and other cancers, is discussed elsewhere. (See "Cancer risks and management of BRCA1/2 carriers without cancer" and "Overview of hereditary breast and ovarian cancer syndromes".)

More detailed information about the approach to screening and risk reduction for breast and ovarian cancer, including the issues of supplemental screening, risk-reducing surgeries, and chemoprevention for those at high risk, is discussed elsewhere.

- (See "Screening for breast cancer: Strategies and recommendations", section on 'Moderate risk: Screening' and "Screening for breast cancer: Strategies and recommendations", section on 'High risk: Screening'.)
- (See "Contralateral prophylactic mastectomy".)
- (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer".)
- (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)
- (See "Management of ovarian cancer associated with BRCA and other genetic mutations".)
- (See "Familial risk factors for pancreatic cancer and screening of high-risk patients".)
- (See "Genetic risk factors for prostate cancer".)

In this topic, we will use the terms "woman/en" or "patient" to describe genetic females. However, we recognize that not all people with breasts and pelvic anatomy that may include a vagina, uterus, ovaries, and/or fallopian tubes identify as female, and we encourage the reader to consider transgender and gender nonbinary individuals as part of this larger group.

CRITERIA FOR GENETIC RISK EVALUATION

Concerning personal or family history — While unaffected individuals often present with concerns about their hereditary cancer risk, whenever possible, it is ideal to initiate genetic testing in a family member who is most likely to test positive for a pathogenic variant, which is usually a woman affected by early breast cancer or ovarian cancer (any age). However, the optimal person to test within a family could also include individuals with other diagnoses such as pancreatic cancer, metastatic breast cancer, or metastatic prostate cancer, even in the absence of a family history of other cancer types [15-17]. (See "Familial risk factors for

pancreatic cancer and screening of high-risk patients" and "Genetic risk factors for prostate cancer".)

Genetic testing in such cases also can affect treatment options (eg, inhibitors of poly[ADP-ribose] polymerase [PARP] are US Food and Drug Administration approved for the treatment of breast cancer susceptibility genes 1 and 2 [*BRCA1* and *BRCA2* (*BRCA1/2*)] carriers with pancreatic, ovarian, or advanced, triple-negative breast cancer). In addition, the phase III OlympiA trial found that adjuvant treatment with olaparib, a PARP inhibitor, extended disease-free survival in patients with inherited *BRCA1/2* pathogenic variants who had high-risk, early-stage, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (table 1 and table 2) [18-20]. Thus, breast cancer patients who may benefit from this treatment are recommended to undergo germline genetic testing. (See "ER/PR negative, HER2-negative (triple-negative) breast cancer", section on 'Patients with previous exposure to chemotherapy'.)

The most commonly implicated pathogenic variants in these types of patients occur in the *BRCA1/2* genes [17], which are inherited in an autosomal-dominant fashion. Data regarding clinical characteristics associated with *BRCA1/2* are discussed elsewhere. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Clinical characteristics associated with BRCA1/2 pathogenic variants'.)

Most patients are offered the option of multigene panel testing, which includes, at a minimum, high-penetrance susceptibility genes: *BRCA1/2*, cadherin 1 (*CDH1*), partner and localizer of *BRCA2* (*PALB2*), phosphatase and tensin homolog (*PTEN*), and tumor protein p53 (*TP53*) [17]. We also include other genes such as ataxia-telangiectasia mutated (*ATM*), checkpoint kinase 2 (*CHEK2*), serine/threonine kinase 11 (*STK11*), and genes associated with Lynch syndrome. Genes associated with lower penetrance may also be included in these panels.

Guidelines from expert groups — Guidelines from the National Comprehensive Cancer Network (NCCN), the American College of Medical Genetics and Genomics, and the National Society of Genetic Counselors provide detailed criteria for identifying other candidates for genetic counseling and testing [21,22], and our approach is consistent with these guidelines.

Key criteria for hereditary cancer risk evaluation and testing include a personal history of the following, among others [22]:

- Breast cancer diagnosed ≤50.
- Breast cancer at any age
  - If results will impact treatment decisions. (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer", section on 'Germline genetic

testing' and "Overview of the approach to metastatic breast cancer", section on 'BRCA 1/2 and PALB2 associated tumors'.)
    - In a male
    - In a person of Ashkenazi Jewish descent
    - That is triple negative histology
    - That is lobular histology in someone with personal or family history of diffuse gastric cancer
    - If there are multiple primary breast cancers (diagnosed at the same time or at different times)
    - If there is also a concerning family history, including any of the following:
        - At least one first-, second-, or third-degree relative with breast cancer ≤50, male breast cancer, ovarian cancer, pancreatic cancer, or prostate cancer that is metastatic or a high- or very high-risk group. (See "Genetic risk factors for prostate cancer".)
        - At least three diagnosis of breast cancer including the patient and/or first-, second-, or third-degree relatives on the same side of the family.
        - At least two first-, second-, or third-degree relatives on the same side of the family with either breast or prostate cancer (any grade).

- Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, any age.

- Exocrine pancreatic cancer, or first-degree relatives of individuals diagnosed with exocrine pancreatic cancer.

- Metastatic prostate cancer, or high/very high-risk prostate cancer, any age. (See "Genetic risk factors for prostate cancer".)

- Prostate cancer diagnosed at any age and Ashkenazi Jewish ancestry.

- *BRCA1/2* or other specific pathogenic variant identified from tumor genomic analysis, regardless of tumor type, if high suspicion for germline origin and confirmation of germline status has clinical implications for the patient or family members. (See 'For those with somatic tumor pathogenic variants or microsatellite instability' below.)

- Family history of cancer only
    - In an individual with a first- or second-degree relative meeting any of the above criteria (unless the affected family member has prostate cancer or pancreatic cancer, in which case only first-degree relatives should be offered testing).
    - In an individual who has a probability of >5 percent of a *BRCA1/2* pathogenic variant based on risk calculators. (See 'Risk assessment models' below.)

Other patients who are also appropriate candidates for testing include:

- Those in whom a pathogenic variant in an actionable gene such *as BRCA1/2* (or other high- to moderate-risk gen*e*s) has been identified in a biologic relative. The extension of testing in families after the identification of a pathogenic variant is called **cascade testing**. For all high-penetrance and many moderate-penetrance gene mutations, it is very important that both male and female r**e**latives be made aware of genetic testing results.

- Testing may be considered in other individuals who have a relatively low probably of testing positive but for whom the identification of a pathogenic variant may affect their management and/or be useful for risk assessment in relatives.

  - For example, female breast cancer diagnosed between ages 50 to 60 in a person with a small family or limited family history information.

- Ashkenazi Jewish adults, even if they have no personal or family history of cancer, may request testing. Although guidelines do not currently recommend systematic testing of such individuals, we offer *BRCA1/2* testing and the option of a multigene panel to individuals who are interested. (See 'Population-based testing for those of Ashkenazi Jewish descent' below.)

Other groups have supported different criteria for genetic testing. For example, the American Society of Breast Surgeons has recommended that genetic testing be made available to everyone with a personal history of breast cancer, in addition to those meeting the NCCN criteria [23]. The NCCN, however, notes that genetic testing in individuals with a low probability of testing positive (<2.5 percent), such as breast cancer patients diagnosed >60 years of age without a family history of breast, ovarian, pancreatic, or prostate cancer, is unlikely to yield results with clinical utility [17].

The United States 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 *BRCA1/2* gene mutations should be assessed with a familial risk-assessment tool (eg, the Ontario Family History Assessment Tool, The International Breast Cancer Intervention Study [IBIS] instrument, or brief versions of BRCAPRO, but not the Gail model) [24]. According to these guidelines, those who have an increased likelihood of a hereditary risk based on such an assessment should receive genetic counseling and, if appropriate, genetic testing, while those without such an indication should not be offered routine genetic counseling or testing. Although no studies have evaluated the effectiveness of genetic counseling and testing in reducing the incidence and mortality of *BRCA1/2*-related cancers, the systematic review on which these guidelines were based included 14 studies (with almost 44,000 patients) that together found moderate to high accuracy of eight risk-assessment tools in predicting the presence of pathogenic *BRCA1/2* variants [25].

In the setting of differing guidelines from expert groups, we continue to support the use of the NCCN criteria as a guide to selecting appropriate individuals for genetic testing, in part because mathematic models may be cumbersome to use in a clinical setting and due to the limitations of family history assessment (eg, unknown family history, small family size, etc). Moreover, many of the risk models assess risk for harboring only high-risk gene mutations (ie, *BRCA1/2*) and do not assess for *PALB2* mutations and less penetrant phenotypes, such as those associated with more moderate-risk genes (eg, *CHEK2*, *ATM*), or other syndromes that are less commonly associated with breast or ovarian cancer, such as Lynch syndrome. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Diagnostic approach'.)

However, the NCCN criteria do not flag all high-risk individuals, and some studies suggest that universal multigene panel testing among patients with solid tumors will increase the detection of heritable pathogenic variants, and influence treatment (albeit in a minority of patients) [26-28]. For example, in one study of nearly 2984 patients with solid tumors undergoing multigene panel testing, pathogenic germline variants were found in 13 percent, including 282 moderate- and high-penetrance cancer susceptibility genes [27]. Nearly 30 percent of patients with high-penetrance variants had modifications in their treatment. In the overall group, a total of 192 patients (6.4 percent) had incremental clinically actionable findings that would not have been detected by phenotype or family history-based testing criteria. More data are needed to refine the genetic testing criteria.

Our considerations for testing recommendations include not only the NCCN guidelines, but also the potential impact of test results on patient management, including treatment, as well as financial factors and implications for relatives. Given that the cost of genetic testing has declined significantly and is affordable for many patients, we believe that discussions around testing should address not only the likelihood of testing positive, but also the potential clinical utility.

For those with somatic tumor pathogenic variants or microsatellite instability — Expert guidelines recommend that patients with metastatic or advanced cancer undergo genomic sequencing if the results would influence management; given site-agnostic drug approvals for cancers with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (*NTRK*) fusions, this provides a rationale for genomic testing for all solid tumors [29].

Tumor testing performed to guide therapy in cancer patients may identify pathogenic variants in a number of genes (eg, *BRCA1/2*) that are also present in the germline, with one study finding that almost one-third of patients with tumor DNA sequencing harbored a germline pathogenic variant [27]. Evidence suggests an association between microsatellite-instable or mismatch-repair-deficient tumors and Lynch syndrome, regardless of primary

tumor type [30]. Thus, confirmatory germline testing is important for patients who receive such results, irrespective of the type of cancer. Such information may affect treatment decisions and may also have important implications for family members.

When such patients are referred to us for confirmatory germline testing, we determine if broader genetic testing with a multigene panel is indicated based on the patient's personal or family history and ancestry, as not all germline variants will also be detected in the tumor [31]. On the other hand, clinically actionable, somatic variants that were first identified in tumors and then confirmed in the germline have occurred in patients who did not meet clinical guidelines for germline testing [30,32]. Thus, panel testing is appropriate for many of these patients.

Of note, while *TP53* mutations are commonly found on tumor profiling, germline mutations are very rare [17,31,33,34]. Thus, unless personal or family history is suggestive of Li-Fraumeni syndrome, we do not obtain germline testing if somatic mutations in *TP53* are detected.

RISK ASSESSMENT MODELS

A number of mathematic models have been developed to ascertain the risk that an individual harbors a pathogenic variant in breast cancer susceptibility genes 1 or 2 (*BRCA1* or *BRCA2* [*BRCA1/2*]) as well as estimate risk of developing breast cancer in women.

- Our preferred model in female patients without breast cancer is the Tyrer-Cuzick model, given its incorporation of family history, as well as its online availability and ease of use. Other models that are helpful in assessing risk in males and females at increased risk owing to a positive family history include BRCAPRO and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA [now called CanRisk]) [35-38].

- Other models that incorporate a first-degree family history of breast cancer and other factors include the National Cancer Institute's Breast Cancer Risk Assessment Tool (BCRAT) and the Breast Cancer Surveillance Consortium's Risk Calculator [35,36,39-41]. However, these two models have been noted to return lower risk estimates in several non-White patient groups, potentially reducing the likelihood of close surveillance or genetic assessment in these patients [42]. A risk prediction model, validated with data from the Black Women's Health Study, may better quantify breast cancer risks in United States Black women, particularly in those under 40 years [43], but should not replace genetic counseling.

- Breast cancer risks derived from BCRAT (Gail model 2) are used in clinical practice [37,39,44], but this model does not capture sufficient family history information for women with more extensive family histories, and thus should not be used to identify candidates for genetic testing.

Because mathematic models may underestimate the likelihood that an individual will test positive for a pathogenic variant in *BRCA1/2*, as well as other related genes, and are somewhat cumbersome to utilize in a traditional clinic setting, we often first use the National Comprehensive Cancer Network qualitative criteria to identify appropriate candidates for genetic testing. (See 'Guidelines from expert groups' above.)

Mathematic models may, however, be very helpful in the following scenarios to provide:

- Breast (and possibly ovarian) cancer risks for women who are low risk and/or who decline genetic testing. (See "Screening for breast cancer: Strategies and recommendations", section on 'Breast cancer risk determination'.)
- *BRCA1/2* mutation carrier probabilities before testing, if required for insurance justification purposes and/or to provide reassurance to low-risk patients.
- Primary or contralateral breast cancer risks, and possibly ovarian cancer risks, after negative (uninformative) *BRCA1/2* gene testing (with or without multigene testing). (See 'Uninformative (negative) result' below.)

In regards to estimating a woman's risk of developing breast and ovarian cancer, most models available for clinical use assume that the cases of hereditary breast/ovarian cancer are attributable to *BRCA1/2* mutations, and thus do not provide probabilities about breast cancer risk based on the chance of testing positive for a moderate-risk or other high-risk pathogenic gene variant. However, the CanRisk model assesses risk for breast and ovarian cancer based on the contribution of several potential gene mutations and nongenetic factors [38]. (See "Screening for breast cancer: Strategies and recommendations", section on 'Clinical use of risk prediction models'.)

Characteristics and limitations of each of these models are discussed in the table (table 3). Of note, none of the models takes into account or has been validated in those with uninformative negative multigene panel results. (See 'Uninformative (negative) result' below.)

PRETEST GENETIC COUNSELING

Traditionally, genetic testing for hereditary cancer was offered after comprehensive genetic counseling and all results were also delivered in the context of genetic counseling. However,

alternative modes of providing genetic testing are increasingly being utilized. In this section, we discuss the indications for and components of genetic counseling, as well as more streamlined models.

Traditional genetic counseling — Whenever possible, patients who are candidates for genetic testing should have the option of undergoing pretest counseling for an individualized genetic risk assessment and discussion of the options for and implications of genetic testing. Pretest counseling may be performed by genetic counselors or other health professionals with expertise in hereditary cancer. Further information about genetic counseling is discussed separately. (See "Genetic counseling: Family history interpretation and risk assessment".)

The following are components of pretest counseling [17]:

- **Medical history and pedigree evaluation –** An important component of pretest counseling is a detailed review of the patient's past medical history and family history, which should include information on maternal and paternal relatives, preferably covering at least three generations. This process is key to not only determining which individuals should undergo genetic counseling, but also is instrumental in ordering the right test and counseling the patient about the rationale for testing and the likelihood of obtaining a positive result. In rare instances, the pedigree reveals the presence of a rare noncancer hereditary syndrome for which specific genetic testing may be indicated. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Cancer risks in BRCA1/2 carriers'.)

- **Mathematic risk assessment models –** Mathematic models may be used to provide patients with estimates of cancer risks and the likelihood of testing positive for a gene mutation [45-47]. These are discussed above. (See 'Risk assessment models' above.)

- **Discussion of genetic testing recommendations –** We most commonly make a recommendation for multigene panel testing that includes high- and moderate-risk genes. We also discuss the option of ordering a larger panel that includes newer genes, for which there is less evidence about risk and management. We discuss potential test result outcomes, including a higher rate of variants of uncertain significance with larger panels. (See 'Selection of initial genetic testing method' below.)

- **Implications of genetic testing –** We discuss the potential benefits, limitations, and risks of testing. We discuss medical management recommendations as well as implications for relatives.

- **Discussion of financial considerations –** For patients considering genetic testing, it is important to address financial considerations. (See "Genetic testing", section on 'Cost

and insurance reimbursement' and "Genetic testing", section on 'Ethical, legal, and psychosocial issues' and "Genetic testing", section on 'Genetic discrimination'.)

In the United States, most insurance companies cover 90 percent or more of the costs of commercial breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2* [*BRCA1/2*]) or multigene panel testing in appropriate candidates. Moreover, several commercial laboratories cap patient out-of-pocket costs (minus a deductible) if testing is covered by insurance. A letter of medical necessity may be required to document the potential impact of a positive test result on surveillance or surgical recommendations for an individual. For patients without insurance, financial assistance programs exist through many labs. In addition, some companies offer self-pay options for multigene testing for $250 or less. In some cases when patients cannot afford testing, testing another family member first may prove useful. If a pathogenic variant is identified, testing relatives for the single variant (or single gene) can be done inexpensively.

- **Discussion of legal protection against genetic discrimination –** One of the primary sources of concern about potential harm in patients undergoing genetic testing stems from their fear of genetic discrimination, which can be a common reason for declining genetic testing [48]. Fortunately, within the United States, federal and state laws provide many protections against genetic discrimination. Additional information on genetic discrimination and legal protection is discussed elsewhere. (See "Genetic testing", section on 'Genetic discrimination'.)

Pretest counseling may be offered in person; however, telephone counseling and telehealth are increasingly utilized as well [49,50]. Two large, randomized studies of telephone versus in-person pre- and post-test *BRCA1/2* genetic counseling showed that the two methods of service delivery are equally safe and effective [51,52]. Although telephone genetic counseling expands access to this service, the uptake of genetic testing has been found to be somewhat lower in women who undergo telephone counseling; however, the reasons for this are unclear [51,52]. Moreover, it is important to assess individuals for distress or anxiety, as certain individuals may be better served by in-person pre- and post-test counseling whenever possible.

Of note, particularly in light of changes to service delivery that occurred during the coronavirus pandemic, video-assisted or telehealth genetic counseling has become increasing popular. Research indicates that such an approach produces similar if not better outcomes compared with telephone-only genetic counseling with respect to factors such as knowledge, patient satisfaction, and psychologic functioning [53,54].

Although psychosocial concerns may deter some high-risk individuals from genetic testing, studies have demonstrated no evidence of major risks for psychological dysfunction in those who pursue testing, including those who test positive for a *BRCA1/2* mutation [55-57].

Therefore, high-risk patients should be encouraged to proceed with testing, particularly if their or their relatives' medical management is likely to be altered by a positive result. High-risk individuals who decline genetic testing should be offered referral to (or ongoing) genetic counseling, access to information regarding genetic testing, and psychological support if they are anxious or distressed [58]. Even if they ultimately do not proceed with testing, these individuals should receive individualized guidelines for cancer surveillance and risk reduction based on their personal and family history.

Alternatives to traditional pretest counseling — The confluence of several factors has resulted in the increased use of streamlined genetic testing service delivery models, particularly for patients with a diagnosis of cancer in whom universal testing is recommended (eg, all patients with ovarian or pancreatic cancer). (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Assessing risk for hereditary syndromes' and "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis", section on 'Testing for hereditary cancer syndromes'.)

These factors include:

- Expanded and frequently updated genetic testing criteria
- The potential impact of positive test results on treatment decisions, particularly in patients who are newly diagnosed
- Increased use of tumor profiling, which may reveal the potential for pathogenic variants in the germline
- The availability of direct-to-consumer genetic testing services

Streamlined genetic testing deviates from the traditional model of offering comprehensive pre- and post-test genetic counseling by a genetic counselor [59].

Such approaches are important given that genetic counseling resources are limited. Several studies have demonstrated that many types of alternative service delivery methods have resulted in substantial increases in testing rates. For example:

- Gynecologic oncologists provided pretest genetic counseling to patients with ovarian cancer and returned negative/uninformative genetic testing results, while referring those with pathogenic variant or variants of uncertain significance to genetic counselors [60].

- Patients with pancreatic cancer obtained pretest education with a video, after which oncology nursing providers offered them genetic testing [61]. Post-test genetic counseling was offered to patients with positive results or a strong family history of cancer.

- Newly diagnosed patients with breast cancer received written pretest information during a surgery appointment and information about how to submit a genetic testing sample [62]. Women with uninformative results received the result by letter, and those with a positive result were scheduled to see a genetic counselor.

SELECTION OF INITIAL GENETIC TESTING METHOD

Suggested approach — For most patients (irrespective of age) meeting National Comprehensive Cancer Network (NCCN) criteria for testing, we offer next-generation multigene panel testing, including for those previously tested without a next-generation multigene panel (typically those tested prior to 2013). Although pathogenic variants in breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2* [*BRCA1/2*]) are most commonly implicated in women with classic signs of hereditary breast/ovarian cancer, approximately 4 to 7 percent have a pathogenic variant in another gene with probable breast and ovarian cancer associations [2-6]. The most common such mutations are in moderate-risk genes, including checkpoint kinase 2 (*CHEK2*), partner and localizer of *BRCA2* (*PALB2*), and ataxia-telangiectasia mutated (*ATM*) [2,5,6,63]. Moreover, multigene panel testing identifies individuals who do not meet criteria for testing for a given syndrome but who, nevertheless, carry pathogenic variants in the associated gene [64]. Some commercial genetic testing companies offer multigene panels that are confined to analysis of high- and moderate-risk gene mutations only, whereas others offer several panel options, including those assessing new, rare, and/or preliminary-evidence genes. (See "Overview of hereditary breast and ovarian cancer syndromes", section on 'Moderate-penetrance genes'.)

This testing can be performed using blood, saliva, or buccal mucosa. Although one option for patients meeting diagnostic criteria for a specific hereditary cancer syndrome (eg, Li-Fraumeni or Cowden) is to test only for mutations in the single associated gene, we typically order a multigene panel for these patients as well, in order to cover other potential differentials, particularly as the cost difference, if any, may be negligible. (See 'Limitations of multigene panel testing' below.)

More limited testing may be an appropriate option in certain contexts, if available; for example:

- For patients who are candidates for multigene panel testing but prefer to minimize the possibility of variants of uncertain significance – Multigene panels may generate data for which the optimal clinical management has not yet been determined, and as such, some patients may opt to have testing performed with a smaller panel of genes (eg, with high- and moderate- risk genes only) for which the cancer risks are better characterized. (See 'Variants of uncertain significance' below.)

- For those of Ashkenazi Jewish descent **without** a personal or family history of cancer – In a clinical setting, requests for testing in this context have been rare; however, with increasing attention about population screening in this ethnic group, the demand is likely to increase. In such patients, we offer testing for pathogenic variants in the *BRCA1/2* genes. This testing includes assessment of three founder mutations, which occur in up to 1 in 40 unselected Ashkenazi Jews [65]. Depending on which laboratory is used, instead of full-gene analysis, testing may be limited to the three *BRCA1/2* founder mutations (185delAG [also known as 187delAG or c.68 69delAG] in *BRCA1*, 5382insC [also known as 5385insc or c.5266dupC] in *BRCA1,* or 6174delT [c.5946delT] in *BRCA2*). Multigene panel testing may also be offered. (See 'Population-based testing for those of Ashkenazi Jewish descent' below.)

    - However, for Ashkenazi Jewish patients **with** a personal or family history suggestive of *BRCA1/2* mutations, we offer the same comprehensive multigene panel testing that we offer non-Jewish patients, given that nonfounder mutations in *BRCA1/2* and pathogenic variants in other susceptibility genes have been observed in 4 to 5 percent of Jewish patients with breast cancer [66,67]. (See 'Limitations of multigene panel testing' below.)

- For patients belonging to a family with a known pathogenic variant, most commonly, based on the laboratory, we offer sequencing of the entire gene in which the variant is identified. However, at a minimum, testing for a single variant is performed. We also offer full *BRCA1/2* testing if the patient has Jewish ancestry.

Offering relatives the option of multigene panel testing is not recommended by national guidelines; however, we do offer it in most contexts given that family history is not always predictive of finding a second mutation, usually from the other side of the family [68]. We make a strong recommendation for panel testing in cases where the proband did not receive panel testing, or the other side of the family is suggestive of hereditary cancer. Although it is rare for an individual to be a double heterozygote or for a family to be segregating more than one pathogenic variant, such cases have been reported [69,70].

Special considerations

Limitations of multigene panel testing — We offer patients whose histories are consistent with *BRCA1/2*-associated cancers the option of pursuing panel testing as first-line testing, as discussed above. (See 'Suggested approach' above.)

Individuals undergoing panel testing must be prepared for the possibility that a high-penetrance variant may be identified even in the absence of a classic presentation of the associated syndrome [71,72]. As a result, highly aggressive interventions may be recommended, such as consideration of upper endoscopic screening and prophylactic

gastrectomy in the setting of cadherin 1 (*CDH1*), even if there are no gastric cancers in the family [71]. In addition, because of the sheer number of genes for which testing may be performed (ranging from 5 to more than 80), the number of variants of uncertain significance (VUS) that may be identified is a concern. The rate of VUS detection also varies based upon the population studied and among laboratories performing the tests. (See 'Variants of uncertain significance' below.)

Finally, in large panels, many of the genes assessed are relatively newly identified. Pathogenic variants in these genes are rare, cancer risks are not well characterized, there are no guidelines for medical management, and the role of predictive testing for family members is uncertain [71,73]. (See "Overview of hereditary breast and ovarian cancer syndromes".)

For those previously tested without next-generation panels — For patients who have previously been assessed for *BRCA1/2* mutations only, we offer re-evaluation using next-generation panel testing, given that this technology has become increasingly available since 2013. This is particularly relevant for patients who meet NCCN criteria for breast, colorectal, ovarian, pancreatic, or prostate cancer susceptibility testing. In addition, patients who were tested for *BRCA1/2* prior to 2006 were unlikely to have had complete analysis of these genes, in that comprehensive assessment for large rearrangements was not performed routinely. Testing with next-generation sequencing is able to identify these rare variants.

Population-based testing for those of Ashkenazi Jewish descent — Given the high frequency of *BRCA1/2* founder mutations in the Ashkenazi Jewish population, there is debate about whether such individuals should be routinely offered *BRCA1/2* testing regardless of personal or family history of cancer. However, as more Ashkenazi Jewish individuals undergo panel testing and other pathogenic variants are identified, it is reasonable to offer this type of expanded testing even in individuals whose only risk factor is their Jewish ancestry. (See 'Criteria for genetic risk evaluation' above and 'Selection of initial genetic testing method' above.)

One population-based study revealed that genetic testing based on family history criteria alone may miss up to one-half of mutation carriers among those of Ashkenazi Jewish descent [74,75]. In this study, 8195 unselected Ashkenazi Jewish men were tested, of whom 175 *BRCA1/2* founder mutation carriers were identified [74]. One-half of these carriers had no significant family history of breast or ovarian cancers. Their female relatives were then offered testing, which revealed 211 mutation carriers. The resulting breast and ovarian cancer risks were similar to those quoted for *BRCA1/2* mutation carriers in the literature. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Cancer risks in BRCA1/2 carriers'.)

A randomized trial of population screening among Ashkenazi Jews in the United Kingdom detected 56 percent more *BRCA1/2* mutation carriers than family history screening alone, and did not result in adverse psychological or quality of life outcomes [76]. In addition, population screening in Ashkenazi Jewish women ages 30 and older has been found to be more cost-effective than family history screening [77].

Thus, population-based testing in Ashkenazi Jews will identify a substantial number of mutation carriers who would not otherwise have been detected, and these individuals could benefit from cancer screening and risk-reducing interventions. (See 'Selection of initial genetic testing method' above.)

Approaches not typically recommended

Germline whole-genome/exome sequencing — Some individuals at very high risk for hereditary cancer do not have a pathogenic variant in a moderate- to high-risk gene, or any of the newer genes assessed on large panels. While it is tempting to consider sequencing of all DNA coding regions (whole-exome sequencing [WES]) or all coding and noncoding DNA regions (whole-genome sequencing [WGS]), available data suggest that such testing is unlikely to yield more actionable results than an expanded panel [78]. Moreover, it is expensive, will yield many VUS and potential false-positive results, and is likely to generate secondary findings unrelated to the testing indication [79-81]. For these reasons, we very rarely recommend germline testing with WES/WGS, and have done so only on a case-by-case basis in individuals with highly striking personal and family histories of cancer and after a negative extended multigene panel test.

Polygenic risk scores — The aggregation of data from several single-nucleotide polymorphisms (SNPs) can be used to generate polygenic risk scores (PRS), and emerging research suggests that these may be useful for cancer risk assessment in general, but also for high-risk individuals who test positive or negative for pathogenic variants in moderate- and high-penetrance genes [82-88]. Although some clinical laboratories have begun to offer PRS, we are awaiting more data about the clinical validity, especially in non-European patients, and clinical utility before integrating it into our practice.

In carriers of high- to moderate-risk pathogenic variants — One large study used PRS to assess breast and ovarian cancer risks in female *BRCA1* and *BRCA2* carriers [83]. The cumulative breast cancer risk estimates between the 10^{th} and 90^{th} percentiles of PRS showed substantial variation in *BRCA1* carriers, with a 56 percent and 75 percent risk by age 80, respectively. For ovarian cancer risk in *BRCA2* carriers, the 10^{th} and 90^{th} percentile lifetime risk of ovarian cancer was 6 percent versus 19 percent, respectively. In the future, this type of individualized risk assessment may be used to better tailor management recommendations, including when to initiate specific types of surveillance, and whether and when to consider risk-reducing surgery.

In another large study, PRS and first-degree family history of breast cancer were used to estimate the lifetime risk of breast cancer in women with pathogenic variants in one of nine high- to moderate-risk genes [88]. This approach found that over one-third of *CHEK2* carriers and about 50 percent of *ATM* carriers had a lifetime risk of under 20 percent. If validated, this information could be used to individualize screening guidelines and better identify carriers who may benefit most from surveillance (eg, with breast MRI) and consideration of risk-reducing surgery.

In individuals with uninformative negative genetic testing results — In individuals with a personal or family history of *BRCA1/2*-associated cancers in which multigene panel testing is negative, it is likely that a combination of SNPs may explain the patient's personal and/or family history of cancer. As an example, over 75 SNPs, conferring an odds ratio for breast cancer of 0.72 to 1.97, have been identified and contribute to approximately 14 percent of breast cancer cases [89]. It is estimated that another 14 percent of breast cancer cases are attributed to unidentified SNPs [89]. In addition, PRS has been combined with other risk factor data or models (eg, Tyrer-Cuzick or The International Breast Cancer Intervention Study [IBIS]) for a more inclusive risk assessment [90]. However, because data are still evolving, we have not integrated PRS scores into the routine risk assessments of patients with uninformative negative results.

Direct-to-consumer BRCA1/2 testing — In March 2018, the US Food and Drug Administration authorized the direct-to-consumer (DTC) company 23andMe to include breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2* [*BRCA1/2*]) testing as part of its Personal Genome Service Genetic Health Risk report [91,92]. Pre- and post-test genetic counseling is not required for individuals interested in such DTC testing.

Any individual who receives a positive result from DTC testing should have it confirmed in a clinical laboratory. Although the likelihood of a false-positive result is very low, it is critical for the result to be confirmed, and an individual, signed report should be provided to the patient. Note that consumers may also obtain their raw genotype data from DTC companies and have it interpreted by a third party. These results yield high rates of false-positive results, including discrepancies about result interpretation, as well as false-negative results [93]. Thus, individuals concerned about hereditary risk should seek professional genetic counseling and the option to pursue clinical genetic testing.

An important concern related to *BRCA1/2* DTC testing is that women at average risk for breast cancer may be falsely reassured about what the genetic testing results mean for their breast cancer risk and the continued need for routine, age-appropriate mammography screening. Additionally, for women with a personal or family history of breast cancer who are candidates for genetic testing, testing only for the founder *BRCA1/2* variants is incomplete, as very few women without Jewish ancestry will test positive for one of these variants.

Additionally, even women of Jewish descent can have another pathogenic variant. Such women need complete *BRCA1/2* gene analysis and are good candidates for multigene panel testing. (See "Personalized medicine", section on 'Direct-to-consumer testing'.)

POST-TEST COUNSELING

Post-test counseling provides an opportunity to review information about hereditary cancer syndromes and for patients to understand and assimilate their results, and to consider next steps if needed. The medical implications of a positive test result are discussed in detail elsewhere. (See "Cancer risks and management of BRCA1/2 carriers without cancer" and "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Cancer risks in BRCA1/2 carriers'.)

An important component of post-test counseling is to inform patients and their family members of the implications of the test result, identify at-risk individuals based upon the pedigree structure, and encourage sharing of this information with relatives. In addition, patients should be provided with information for their relatives (eg, copies of the test result and information on how to find a genetic counselor). Finally, they should stipulate when, if ever, they would disclose results without patient consent. Clinicians should document that patients are informed about who in their family is at risk for hereditary cancer and what the potential implications are. Ethical and legal considerations are discussed elsewhere. (See "Genetic testing", section on 'Disclosure to family members'.)

APPROACH TO POSITIVE TEST RESULTS

A positive result means that a pathogenic (ie, deleterious or harmful) variant was identified in a gene such as breast cancer susceptibility gene 1 or 2 (*BRCA1* or *BRCA2*). Most of these variants are protein truncating, while others may result in an abnormal amount or conformation of gene product (protein). Some pathogenic variants are unique to individual families, whereas others have been reported in several different families.

The cancer risks for and management of individuals with a positive result are discussed elsewhere. (See "Overview of hereditary breast and ovarian cancer syndromes" and "Cancer risks and management of BRCA1/2 carriers without cancer".)

APPROACH TO NEGATIVE OR UNINFORMATIVE RESULTS

Definitions

True-negative results — A true-negative result means that a pathogenic variant that has been identified in a patient's family member (usually a first- or second-degree relative such as a parent, sibling, aunt or uncle) has been ruled out in the tested individual. An example of this type of result would be when the child of a parent with a pathogenic variant in *BRCA1* or *BRCA2 (BRCA1/2*) mutation tests negative for that mutation.

- Women with a true-negative *BRCA1/2* test result are generally counseled that their risk of breast and ovarian cancer is the same or possibly slightly higher than the general population [94-98]; the risk estimates, however, may be modified based upon other risk factors, such as suggestive family history of the noncarrier parent and traditional reproductive risk factors. A higher rate of breast cancer in noncarriers may be related to genetic modifiers, including single-nucleotide polymorphisms (SNPs) [94].

- Men with a true-negative result and a family history of prostate cancer including one or more affected men who were not genetically tested may still have an elevated risk of developing this cancer. We counsel them about the uncertainty in their risk and provide empiric data about possible prostate cancer risks based on family history. (See "Genetic risk factors for prostate cancer".)

- Similarly, individuals with a true-negative result and a family history of pancreatic cancer including one or more affected individuals with this cancer who were not genetically tested may still have an increased risk of developing this cancer. We counsel them about the uncertainty in their risk and provide empiric data about possible pancreatic cancer risks based on family history. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients".)

- It is less clear how to interpret negative test results in families with a pathogenic variant in a moderate-risk gene such as checkpoint kinase 2 (*CHEK2)* or in rare genes such as *RAD50.* In these families, it is often not possible to know whether the identified variant led to the cancers in the family, or whether other gene variants or SNPs could be contributing to increased cancer risks as well. Thus, in families with these types of moderate-risk gene variants, genetic testing in at-risk individuals may not provide a definitive answer about cancer risk or whether management should be altered [99,100]. Whether further testing is indicated depends on the situation and the individual's risk, as well as which test was done. (See 'Uninformative (negative) result' below.)

Further discussion of these moderate-risk genes is found elsewhere. (See "Overview of hereditary breast and ovarian cancer syndromes", section on 'Moderate-penetrance genes'.)

Uninformative (negative) result — There are two types of uninformative results. The first occurs when genetic testing results do not indicate the presence of a pathogenic variant, and

there is no known cancer susceptibility pathogenic variant in the family. The second is when one or more variants of uncertain significance (VUS) are identified. (See 'Variants of uncertain significance' below.)

The first type of uninformative negative result may be due to a number of possibilities that depend, in part, on what testing was performed. The possibilities include:

- A pathogenic variant could be present in one of the genes for which testing was performed, but it cannot be detected by available methods. With advances in technology, these types of variants are thought to be rare.
- A pathogenic variant may be present in a gene for which testing was not performed or in a gene not yet identified. If there is strong clinical suspicion of a hereditary syndrome, multigene panel testing would be indicated.
- Combinations of SNPs associated with increased cancer risk may be present.
- If an unaffected individual is the first to be tested in a family, a negative result could mean that they did not inherit a pathogenic variant that may be present in other relatives, or the result could be due to one of the explanations above.
- It is possible for sporadic cancers, such as breast cancers, to occur within families who have an identified pathogenic variant. When this occurrence can be documented, the affected individual is said to be a "phenocopy," which refers to a noncarrier in a family known to harbor a pathogenic variant in genes such as *BRCA1/2*. Thus, if the first affected individual to be tested in a family receives a negative result, it may still be recommended to offer testing to another individual in the family, preferably one with a genetically related cancer.

Variants of uncertain significance — When a gene alteration is identified but its clinical significance is unclear, this is termed a VUS. In this instance, it is unclear if the variant is an undefined pathogenic variant, a benign polymorphism (ie, normal change in the gene), or a variant with an intermediate risk of cancer [101,102]. Some individuals may test positive for a pathogenic variant and still have one or more VUS results. For individuals lacking a pathogenic variant, in whom one or more VUS are identified, the result is considered uninformative. Such individuals should be managed based upon their personal and family history, and should **not** be counseled as though the variant is pathogenic.

Given the high rate of VUS obtained from multigene panel testing, patients must be informed that such findings are expected, and, that over time, many VUS will be reclassified. Standard criteria, determined by professional societies as well as functional, epidemiologic, and clinical parameters, are used to determine if a VUS can be reclassified as a normal or harmful change in the gene [4,102]. ClinVar is an open access database of variant

classifications available through the National Library of Medicine [103]. Although it is a helpful resource, it should not be used independently of laboratory generated data to interpret VUS results given that discordant classifications are not rare [104,105]. VUS usually are downgraded to benign or likely benign variants [106]. However, a small number of VUS get reclassified in such a way that clinical management is altered [107]. Thus, providers must review VUS reclassifications when obtained from the laboratory (or inquire about reclassification when appropriate) and notify patients accordingly. We also advise patients to keep us informed of their current contact information in the event an amended report is issued.

Based upon 20 years of experience and more than one million samples tested for a deleterious *BRCA1/2* mutation, the rate of identification of a VUS within a major United States laboratory was reported to be 2.1 percent, a decrease of 84 percent over the prior decade [102]. The VUS rate in *BRCA1/2* is higher in certain ethnic groups such as individuals who are of African or Middle Eastern descent [102]. It is important to note that the higher the number of genes assessed (ie, as part of a multigene panel test), the more VUS will be identified. For example, in a study of 9187 patients with breast, colorectal, ovarian, pancreatic, or prostate cancer tested with a 76 or 88 germline gene panel, one or more VUS were found in 57 percent of the patients [108].

Patients with VUS (or positive) results from multigene testing may participate in an online registry called Prospective Registry of Multiplex Testing (PROMPT), a collaborative effort among academic institutions and commercial laboratories in the United States to study and reclassify these types of results [109]. (See "Genetic testing".)

In some clinical settings, relatives of the patient with a VUS may be tested for clinical research to track the variant in the family, the data from which may be useful in aggregate to reclassify the variant.

Breast cancer risk management — As discussed, additional genetic testing may be warranted for some patients with uninformative negative or VUS test results in the form of more extended multigene panels.

However, for those who do not pursue additional testing or for whom additional testing is also uninformative, determining an individual's risk of developing cancer can be challenging, and it is highly dependent on the family history, an individual's own cancer history and risk factors, and the type of testing performed. Our approach is outlined in the sections below.

No personal history of breast cancer — For women who have not had cancer, breast cancer risk should be evaluated by age 30 [110]. Mathematic tools may be used to assess their risk of breast cancer, and these may be selected based on their appropriateness in individual circumstances. In our practice, we often use both the BRCAPRO and the Tyrer-

Cuzick models to provide a range of breast cancer risks. The BRCAPRO model often predicts average to slightly elevated breast cancer risks compared with the general population, for those with an uninformative *BRCA1/2* test. On the other hand, although the Tyrer-Cuzick model is well validated, in our experience, the predicted risks are often much higher than other quantitative models, as has been reported elsewhere [111]. (See 'Risk assessment models' above.)

The approach to breast cancer risk management depends upon whether women are deemed to be at high risk or average risk.

Women at high risk — Women deemed to be at high lifetime risk of breast cancer (defined as a risk of at least 20 percent) should undergo annual screening mammogram, annual breast magnetic resonance imaging (MRI), and at age 21, clinical breast exam every 6 to 12 months. Imaging should begin 10 years prior to the age at diagnosis of the youngest affected family member but not prior to age 30 for mammography and not prior to age 25 for MRI [112]. For example, if a woman meeting the risk threshold has a sister with breast cancer diagnosed at age 30, MRI beginning at age 25 may be recommended. (See "Screening for breast cancer: Strategies and recommendations", section on 'High risk: Screening'.)

Women with a life expectancy of at least 10 years may also consider risk-reduction options. For example, women with a five-year breast cancer risk of at least 1.7 percent or a 20 percent lifetime risk of cancer may consider chemoprevention with agents such as tamoxifen, raloxifene, or an aromatase inhibitor, which reduce breast cancer risk by about 50 percent [113]. While chemoprevention has not been well studied in women with uninformative negative genetic testing results, we approach these discussions based on the data obtained from trials of these agents in the general population. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

Women at very high risk of breast cancer and uninformative negative test results may wish to discuss the option of risk-reducing mastectomy.

Women not at high risk — Women with lifetime breast cancer risks under 15 percent may be screened as per the general population, or somewhat more aggressively depending on their specific risk [112]. Owing to limitations in quantitative risk assessment, early initiation of screening may be recommended based on family history. (See "Screening for breast cancer: Strategies and recommendations".)

Personal history of breast cancer — Women with a personal history of breast cancer have a risk of contralateral breast cancer (CBC) of about 4 to 7 percent in the first 5 to 10 years after diagnosis [114]. Those with a personal and family history have a higher risk, even with an uninformative negative *BRCA1/2* test result [115-117]. These risks are even more

substantial for younger women. (See "Factors that modify breast cancer risk in women", section on 'Personal and family history of breast cancer'.)

While models such as BRCAPRO can generate estimates of breast cancer risk in *BRCA1/2*-negative women, these tools have not been validated for CBC risk assessment. Nevertheless, we do run the BRCAPRO model in order to give patients a sense about their level of risk for a CBC.

For some breast cancer survivors with a family history of breast cancer, their lifetime risk of developing a CBC may make them good candidates for heightened surveillance with breast MRI in addition to mammography. Although a panel convened by the American Cancer Society concluded that there was insufficient evidence to recommend for or against MRI in breast cancer survivors [118], MRI may be appropriate for screening survivors with other risk factors, such as those related to breast cancer subtype, age at diagnosis, or reproductive or family history [17,110,112,119]. Studies are needed to determine whether MRI screening in breast cancer survivors is associated with mortality reduction. (See "Approach to the patient following treatment for breast cancer", section on 'Breast imaging'.)

As an alternative to surveillance, women with high risk for CBC may consider a bilateral mastectomy as their definitive treatment, with the contralateral mastectomy performed at the time of diagnosis or at a later point. While some studies had suggested a survival benefit to this procedure, this was likely driven by selection bias, and subsequent studies have not demonstrated survival benefit for contralateral prophylactic mastectomy [120]. It is also important to note that if these women receive adjuvant endocrine therapy for hormone receptor-positive disease, they would derive about a 50 percent reduction in risk of developing a new breast cancer. (See "Contralateral prophylactic mastectomy".)

Ovarian cancer risk management

No family history of ovarian cancer — Women with no family history of ovarian cancer and negative genetic testing results are usually considered to be at average risk of ovarian cancer and are not candidates for ovarian cancer screening.

Although unselected women with a prior history of breast cancer have historically been reported to have a slightly increased risk of ovarian cancer [121], it is likely that most of that risk can be attributed to pathogenic variants in susceptibility genes such as *BRCA1/2* [122]. In families with breast cancer but without ovarian cancer or another hereditary syndrome, there does not appear to be an increased risk of ovarian cancer [96,123,124].

For women without a family history of ovarian cancer in whom pathogenic variants in genes associated with increased risks of ovarian cancer are ruled out (especially *BRCA1/2*), we do not offer risk-reducing bilateral salpingo-oophorectomy (rrBSO) for risk reduction (even if a strong family history of breast cancer is present).

Risk assessment for all women should take into account other risk factors associated with ovarian cancer, such as infertility, reproductive factors, and hormonal use. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors".)

Family history of ovarian, primary peritoneal, or fallopian tube cancer — When a woman with a family history of ovarian cancer tests negative for a panel including genes in which pathogenic variants are associated with ovarian cancer, her risk of ovarian cancer may still be elevated relative to the general population [125]. As such, our approach to women with negative genetic testing and a family history of ovarian cancer is summarized below:

- We counsel that oral contraceptive use in premenopausal women may significantly reduce the risk of ovarian cancer, particularly with long-term use and regardless of family history and/or a recognized genetic predisposition to the disease [126,127]. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer", section on 'Chemoprevention'.)

- Women at increased risk of ovarian cancer, particularly if they are postmenopausal and are undergoing hysterectomy for benign reasons, may also be offered rrBSO. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer", section on 'Candidates' and "Elective oophorectomy or ovarian conservation at the time of hysterectomy".)

- We counsel about the limited effectiveness of available screening for ovarian cancer, which includes cancer antigen (CA) 125 blood tests and transvaginal ultrasound, and that this approach is generally not advised. (See "Screening for ovarian cancer".)

This approach is based on epidemiologic data suggesting increased ovarian cancer risks among women with a family history of ovarian cancer. For example, studies suggest that women who have one first-degree relative with ovarian cancer have about a 5 percent risk of ovarian cancer, a 3.5 percent risk if she has one second-degree relative, and a 7 percent risk of ovarian cancer if she has two affected relatives [126,128]. However, some of this risk may be due to pathogenic variants in *BRCA1/2* and, to a lesser extent, in other genes associated with ovarian cancer (eg, RAD51 paralog C [*RAD51C*], RAD51 paralog D [*RAD51D*], *BRCA1*-interacting protein 1 [*BRIP1*]). We counsel women with negative genetic testing and family history of ovarian cancer that their risk of ovarian cancer may be elevated relative to the general population, but we take into account the overall suggestiveness of the family history when making management recommendations.

Management of women with a personal history of ovarian cancer is discussed elsewhere. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Surgical staging".)

Screening for prostate cancer — Men with a family history of prostate cancer and uninformative negative genetic testing results that include *BRCA1/2* testing at a minimum

should be assessed for risk based on race, age, and family history, and managed accordingly. (See "Screening for prostate cancer".)

Screening for pancreatic cancer — Individuals with a family history of pancreatic cancer and uninformative negative genetic testing results that include *BRCA1/2* and other genes in the differential (eg, Lynch syndrome) should be assessed for risk based on family history and other factors. Screening may be appropriate for some individuals. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary breast and ovarian cancer" and "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Genetic testing for breast, ovarian, prostate, and pancreatic cancer (The Basics)" and "Patient education: Genetic testing (The Basics)")
- Beyond the Basics topics (see "Patient education: Genetic testing for hereditary breast, ovarian, prostate, and pancreatic cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Introduction –** Although most breast, ovarian, prostate, and pancreatic cancers are sporadic, a minority are caused by germline mutations in breast cancer susceptibility

gene 1 or 2 (*BRCA1* or *BRCA2* [*BRCA1/2*]). Other inherited pathogenic variants account for a smaller percentage of these cancers. (See 'Introduction' above.)

- **Criteria for genetic risk evaluation** – Key criteria for genetic risk evaluation include, among others, personal history of female breast cancer diagnosed ≤50 years, triple-negative breast cancer, or personal or family history of ovarian cancer, male breast cancer, metastatic prostate cancer, or exocrine pancreatic cancer. Alternatively, some experts suggest universal testing of all patients with breast cancer. Patients who are candidates for genetic testing should have the option of being referred to a credentialed genetics provider for pre- and post-test education. Increasingly, alternatives to traditional pretest education and counseling are being offered. (See 'Criteria for genetic risk evaluation' above.)

- **Selection of initial genetic testing method** – We offer most patients whose histories are consistent with hereditary cancer the option of pursuing multigene panel testing as first-line testing. (See 'Selection of initial genetic testing method' above.)

  - High-risk patients who previously underwent *BRCA1/2* testing and who desire additional genetic testing should be counseled regarding the chance that they may harbor either a rare undetected *BRCA1/2* pathogenic variant (if tested before 2006) or a pathogenic variant in another gene, and should be offered next-generation panel testing. (See 'For those previously tested without next-generation panels' above.)

- **Approach to positive results** – The cancer risks for and management of individuals with a positive result are discussed elsewhere. (See "Overview of hereditary breast and ovarian cancer syndromes" and "Cancer risks and management of BRCA1/2 carriers without cancer".)

- **Approach to negative or uninformative results**

  - For women with negative or uninformative test results, quantitative models can help identify women with a high lifetime risk of breast cancer of at least 20 percent. These women are candidates for breast cancer screening with magnetic resonance imaging in addition to mammography. (See 'Risk assessment models' above and 'No personal history of breast cancer' above and "MRI of the breast and emerging technologies", section on 'Screening high-risk women'.)

  - Women with uninformative negative genetic testing results without a family history of ovarian cancer do not appear to be at increased risk of developing ovarian cancer. Thus, bilateral salpingo-oophorectomy is not indicated for ovarian cancer risk reduction. (See 'No family history of ovarian cancer' above.)

- Individuals who have a family history of prostate or pancreatic cancer and who have true-negative or uninformative genetic testing results may still be at increased risk for these cancers and should undergo an individualized risk assessment and a discussion about the potential benefits, limitations, and risks of screening for these cancers. (See "Screening for prostate cancer" and "Familial risk factors for pancreatic cancer and screening of high-risk patients".)

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Topic 753 Version 63.0

GRAPHICS

High-risk criteria according to the OlympiA trial[1]

Triple-negative breast cancer (82% of patients):
▪ If treated with adjuvant chemotherapy, were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathologic analysis.
▪ If treated with neoadjuvant chemotherapy, were required to have residual invasive breast cancer in the breast or resected lymph nodes (ie, no pCR from neoadjuvant therapy).
Hormone receptor-positive breast cancer (18% of patients):
▪ If treated with adjuvant chemotherapy, were required to have at least 4 pathologically confirmed positive lymph nodes.
▪ If treated with neoadjuvant chemotherapy, were required to have not had a pCR with a CPS+EG score of 3 or higher.[2,3] The CPS+EG scoring system estimates relapse probability on the basis of clinical and pathologic stage (CPS) and estrogen receptor status and histologic grade (EG); scores range from 0 to 6, with higher scores indicating worse prognosis.

pCR: pathologic complete response.

Reference:

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Graphic 131856 Version 3.0

CPS + EG score calculation

Stage or feature	Points
Clinical stage (AJCC staging[1])	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic stage (AJCC staging[1])	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Receptor status	
ER-negative	1
Nuclear grade*	
Nuclear grade 3	1

CPS + EG score calculation instructions: Add the points for clinical stage + pathologic stage + ER status + nuclear grade to derive a sum between 0 and 6.

CPS + EG: clinical stage + pathologic stage + ER status + nuclear grade; ER: estrogen receptor; AJCC: American Joint Committee on Cancer.

* In the unlikely situation nuclear grade cannot be determined, regular histologic grade should be used; if only Nottingham overall grade is reported, the Nottingham overall grade must be 9 to be scored as 1 point in the CPS + EG score.

From: Tutt AN, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med 2021; 384:2394. Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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1. AJCC (American Joint Committee on Cancer): Cancer Staging Manual, 8th ed, Springer, 2017.

Graphic 132498 Version 1.0

Breast cancer risk prediction tools

Model	Characteristics and limitations
Gail model 2 (BRCAT)[1]	Considers nongenetic risk factors such as age at menarche, first term birth, and biopsy history, including atypical hyperplasia. Not appropriate for females with DCIS, LCIS, prior chest radiation due to Hodgkin lymphoma, or for females with *BRCA 1/2* mutations.
	Does not consider family history beyond first-degree relatives with breast cancer. It does not factor in any other cancers or any paternal relatives with cancer.
	Calculates 5-year and lifetime invasive breast cancer risk.
Breast cancer surveillance consortium Risk Calculator[2]	Considers age, race, family history of breast cancer in a first-degree relative, breast biopsy history, and mammographic breast density.
	Does not consider family history beyond first-degree relatives with breast cancer. It does not factor in any other cancers or any paternal relatives with cancer.
	Calculates 5- and 10-year invasive breast cancer risk.
Tyrer-Cuzick (IBIS)[3]	Considers nongenetic risk factors such as age at menarche, first term birth, biopsy history, height and weight, age at menopause, etc.
	Considers a family history of breast and ovarian cancer beyond first-degree relatives.
	Although it considers the contributions of other low-penetrance genes to breast cancer risk,[4] some evidence suggests it overestimates the risk of subsequent breast cancer, except in those with personal or family history of *BRCA 1/2* mutations.[5]
	Not used in patients with a history of breast cancer.
	Often predicts breast cancer risks that are higher than other mathematic models.
	Calculates 10-year and lifetime invasive breast cancer risk and the risk of carrying a *BRCA 1/2* mutation.
Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA, now called CanRisk)[6]	Considers age, BMI, alcohol consumption, number of children and age at first birth, mammographic breast density, personal cancer history, results of genetic testing (if available), and family history.
BRCAPRO (part of CancerGene)[7]	Considers race, Ashkenazi Jewish ancestry, as well as extensive family history of breast, ovarian, and other cancers and constructs a pedigree.
	Considers history of oophorectomy and bilateral oophorectomy.
	Contains the Chen-Gail model, which estimates breast cancer risk on Gail model factors plus weight and mammographic density; however, this

	model is not well validated.[8]
	Assumes that *BRCA 1/2* mutations account for all hereditary breast and ovarian cancers.[7,9]
	In the highest-risk families (eg, with multiple cases of ovarian cancer and early breast cancer), the model may generate high residual risks for carrying a *BRCA* mutation (ie, the chance of carrying an undetected pathogenic variant). Thus, it may generate high risks for primary or contralateral breast cancer and ovarian cancer, even with an uninformative negative result.
	Calculates probability of having a *BRCA 1/2* mutation.

DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; BRCA: breast cancer susceptibility genes.

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Graphic 118958 Version 4.0

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