

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

Purpose

To outline recommendations for genetic testing that medical professionals can use to assess hereditary risk for breast cancer in their patients.

Methods

Literature review included large datasets, basic science publications, and recent updated national guidelines. This is not an exhaustive systematic review, but a comprehensive review of the most impactful evidence in the modern literature on this subject. Genetic testing to assess hereditary risk of cancer is a broad and dynamic area of medical research. The dominant focus of this guideline is limited in scope to breast cancer. Similar guidelines have been previously put forth from this body in 2006, 2012, 2016, and 2017.

Approval

Please see list of Authors and Disclosures at the end of the statement. This consensus statement was developed under the direction of and approved by the ASBrS Board of Directors.

Recommendations

- Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing.** When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes.
- Genetic testing should be made available to all patients with a personal history of breast cancer.** Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment

recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies.

3. **Patients who had genetic testing previously may benefit from updated testing.** Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing.¹ Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2.
4. **Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines.** Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of “uninformative negative” results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above.
5. **Variants of uncertain significance are DNA sequences that are NOT clinically actionable.** This type of result needs to be considered as inconclusive, and the patient should be managed based on their risk factors and not influenced by this result.

Summary of Data Reviewed

The National Cancer Institute estimates for 2018 were that more than 266,000 new cases of invasive breast cancer would be diagnosed in the United States, and more than 40,000 patients would die from the disease.² Approximately 10% of breast cancers are associated with a pathogenic germline variant in one of several different genes.³ More than 50% of pathogenic germline variants are mutations in the BRCA1 and BRCA2 genes.⁴⁻⁹ Using genetic testing to identify patients who are at increased risk to develop breast cancer enables patients to take steps to reduce this risk. There are several risk management strategies available for individuals at increased risk (e.g., chemoprevention along with enhanced screening; risk reducing surgeries).¹⁰⁻¹⁸ **Unfortunately, in the current state of medical practice, a significant number of pathogenic mutation carriers remain undetected and undiagnosed. These are largely women with “moderate penetrance” mutations, but even women with BRCA1 or 2 mutations may not be identified.**¹⁹⁻²⁰ There is an unmet challenge to improve our identification and diagnosis of patients who have an inherited increased lifetime risk of breast cancer.

Access to Genetic Counseling and Testing

There are fewer barriers to genetic testing now than previously, and testing is less costly and being offered by more labs. The indications for who should be offered testing are ever increasing - each guideline update casting a wider net, and there is more public awareness. However, some barriers remain - one of which is the limited availability of genetic counseling nationwide for patients and their family members.¹⁹⁻²⁰

Increased access to testing would likely lead to more patients pursuing testing and improving rates of identification of gene carriers. Breast surgeons are well positioned to be a resource for patients who may benefit from testing. Breast surgeons can identify individuals who are suitable for testing, inform patients of the risks and benefits, provide access to genetic testing, and also discuss risk management strategies for those patients who test positive. For patients with less common mutations, strong consideration should be given to consultation with cancer genetics specialists.²¹⁻²³

Hereditary Breast Cancer Syndromes

Hereditary mutations to be considered include BRCA 1&2, PALB2, and other hereditary breast cancer syndromes, which include but are not limited to Li-Fraumeni syndrome (TP53 pathogenic variant), Cowden syndrome (PTEN pathogenic variant), Hereditary diffuse gastric cancer syndrome (CDH1 pathogenic variant), and Peutz-Jegher syndrome (STK11 pathogenic variant).

Impact of genetic testing results on management recommendations

Identification of patients with pathogenic variants in these genes can influence patient management in terms of high-risk screening and risk reduction as well as therapeutic options related to surgery, radiation, and systemic therapies.²⁴⁻²⁶ For example, identifying that a breast cancer patient has a BRCA1 pathogenic variant provides that patient the opportunity to learn of her elevated risk for contralateral breast cancer as well as of ovarian cancer and to make educated decisions to reduce those risks.²⁶ Studies are underway to determine whether these patients also might benefit from PARP inhibitors being included in their adjuvant therapy regimen. Another example is that radiation is relatively contraindicated in patients with TP53 pathogenic variants (associated with Li-Fraumeni Syndrome) due to their increased risk of developing radiation-induced secondary malignancies.

Identifying a patient who has a pathogenic variant that indicates high hereditary breast cancer risk can have a profound impact on that patient's health and management. Additionally, it has potential impact on that patient's family members who should be counselled to consider testing for the mutation identified in the family, the result of which can guide their risk of breast cancer development and consideration of risk management strategies.

The genetic testing information should be considered together with the details of each patient's case including age, family history, medical history, and contributing risk factors, as

well as careful review of existing management guidelines. It is important to understand that risk of development of breast and other cancers and risk management guidelines vary both by the mutated gene and the penetrance of the specific genetic mutation. Additionally, not all pathogenic variants identified are medically actionable.

Just because a hereditary pathogenic mutation that predisposes to breast cancer is identified does not mean that the risk-reducing mastectomy is indicated. Risk-reducing mastectomy can be considered in BRCA1, BRCA 2, PTEN, and TP53. Consideration may also be appropriate for patients with mutations in other genes when combined with a significant family history of breast cancer.

Patients with BRCA1 or BRCA2 pathogenic variants should consider risk-reducing bilateral salpingo-oophorectomy after child-bearing or between the ages of 35-40 to reduce ovarian and fallopian tube cancer risk. Women with BRCA1 should consider oophorectomy between ages 35-40, while BRCA2 carriers should consider it between ages 40-45.

Prophylactic oophorectomy in premenopausal women with BRCA2 pathogenic variants has also been shown to reduce the risk of breast cancer by about 50%. There is also breast cancer risk reduction from RRSO in BRCA1 patients but to a lesser degree.^{10,11,17}

For patients with mutations in ATM, CDH1, CHEK2, NBN, NF1, PALB2, and STK11, enhanced screening is recommended; however, currently the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as a strong family history. There are substantial gaps in our ability to predict individual risks associated with mutations in some of these genes. Risk is modulated by age, family history, and in some cases, the specific mutation in a particular gene. For the aforementioned syndromes, the guidelines broadly support considering mammography with tomosynthesis and breast MRI with and without contrast for annual screening due to the elevated risk for breast cancer.

For BARD1, MSH2, MLH1, MSH6, PMS2, EPCAM, BRIP1, RAD51C, RAD51D, there are some data suggesting an elevated lifetime risk of breast cancer; however, there is insufficient evidence to support change in breast cancer risk management based on the presence of a mutation alone. Mutations in these genes may be associated with an increased risk of gynecological cancers, which may warrant specific management. MSH2, MLH1, MSH6, and PMS2 are associated with the Lynch Syndrome, a multi-organ predisposition syndrome that requires multidisciplinary management.

The list of actionable genes and recommendations for screening and risk management continually evolves as additional information becomes available. We refer the readers to the NCCN guidelines, available online at www.nccn.org under the title Familial High-Risk Assessment: Breast and Ovarian Cancer (most recently updated in early 2019). The All Syndromes Known to Man Evaluator (<https://ask2me.org/>) is another tool available with information on the spectrum and estimated penetrance for pathologic variants.²⁷

Limitations of genetic testing

Health care providers and patients need to know that genetic testing is one of several tools for assessing breast cancer risk. Not every genetic test yields a straightforward answer with clear guidance on how to proceed for optimal care. Patients should be made aware that negative test results do not necessarily mean they are not at increased risk for developing breast cancer.

Many factors contribute to a patient's lifetime risk of breast cancer, and genetic testing is an effort to better define one of these elements (the measurable inherited risk). When counseling patients about their lifetime risk of breast cancer, it is critical to look broadly at the patients' other contributing factors, some of which are: age, medical history, lifestyle, exposures, and family history. For patients who test positive for a pathogenic variant, it is important to gain detailed understanding of that variant when advising on risk management strategies – details such as the penetrance of the cancer risk among carriers (how likely is the patient to actually develop breast cancer). Penetrance varies among the identified hereditary cancer syndromes. In other words, not all carriers of pathogenic genetic variants will develop breast cancer, and the level of risk varies with the gene affected and likely the variant as well.^{6,28,29}

For example, some types of CHEK2 and ATM variants have low penetrance while other types are more highly penetrant.^{30,31} Just because a patient tests positive for a hereditary breast cancer syndrome does not mean that patient will develop breast cancer. ask2me.org can be useful in understanding the penetrance and the management for most cancer-causing genes, and the BRCA Decision Tool, <http://brcatool.stanford.edu/brca.html>, can be useful in known BRCA pathogenic variant carriers to predict likelihood of developing breast or ovarian cancer and likelihood of dying from either disease based on patient age and a variety of interventions chosen for screening and prophylaxis. It is important to note that these calculators are constrained by the limitations of the studies that provide the underlying odds ratios used to generate the absolute risk estimates and do not account for modification of those odds ratios by age, mutation position, family history, or polygenic background risk.³²

Pre-and Post-test Counseling

Before testing, patients need to be made aware of the implications that the test result can have (pre-test counseling); and when results become available, patients should be reminded of these implications and be provided the appropriate clinical context for the results to make informed decisions (post-test counseling). All genetic testing should be performed in the setting of informed consent. The American College of Surgeons Commission on Cancer accreditation program mandates that cancer risk assessment, counseling, and genetic testing services be provided to patients by a physician who does risk assessment regularly and/or is qualified to do testing or a qualified genetic professional either on site or by referral.³³ A systematic review of the literature indicates that pre-test counseling, whether by a geneticist, breast surgeon, oncology nurse, or other medical professional with expertise and experience in cancer genetics reduces distress, improves risk perception accuracy, and improves follow through for testing.³⁴ Breast surgeons who are knowledgeable in cancer genetics can initiate and guide genetic testing for their patients. Pre-test counseling should include discussion of

the types of results (true positive = pathogenic, true negative = benign (although without a known positive in a family, it may also be inconclusive as well), and inconclusive = variant of uncertain significance (VUS)). Other potential issues of testing should also be reviewed, such as inconclusive results, misperception of true risk, and discrimination. As noted above, patients need to know there are limitations to this testing including non-informative results or negative tests as well as the reality of the evolving science. It is important to educate patients on the benefits of testing as a vehicle to knowing better their individual risk and empowerment to consider interventions to manage or reduce that risk. It can be helpful to set expectations for when the test results will be available.

Post-test counseling is important regardless of the actual result. The current best practice is for all patients who undergo genetic testing to have some form of post-test counseling. By NCCN guidelines, this can occur in person or remotely. This allows for patients' questions to be answered and for a thorough debriefing. If a result is negative or non-informative (such as a variant of uncertain significance – VUS) then the patient's other risk factors for breast cancer (age, medical history, family history, etc.) need to be evaluated to formulate the appropriate risk management plan. Depending on the level of risk for breast cancer, strategies to manage that risk can be discussed, including enhanced screening imaging (annual mammogram and breast MRI); chemoprevention (endocrine therapy to lower risk); lifestyle modification with respect to obesity, tobacco use, and alcohol consumption; and exogenous hormone use among others.

For patients who test positive for a pathogenic variant, a clear review of the state of evidence for that specific syndrome is imperative. To make educated decisions, patients need to know about the spectrum of risk management strategies. Ultimately, a customized plan for the patient is the goal with their informed consent. In this discussion, a frank statement of the level of risk reduction for each intervention is needed. For example, risk-reducing mastectomy and reconstruction in a BRCA1-positive 35-year-old patient leads to much greater risk reduction for breast cancer mortality than that same intervention in a 65-year-old patient.^{21,35,36} The surgeon should discuss these issues and refer to other specialists (such as gynecologic oncologists, gastroenterologists, etc.) for other organs at risk as appropriate. For complex scenarios, referral to a genetics professional is recommended.

Multi-gene Panel Testing

Genetic testing has expanded in scope and availability since 2013 when the U.S. Supreme Court ruling in *Association for Molecular Pathology v. Myriad Genetics, Inc.* increased the testing options. Increased competition has helped to lower the cost. Improvements in technology, like next-generation sequencing, has made testing for more than one gene at a time a reality.³⁷⁻⁴¹ which can improve the cost-effectiveness and efficiency of testing. While BRCA1 and BRCA2 remain the most likely genes to be mutated in a family with high breast and ovarian cancer risk, panel testing can allow for more comprehensive coverage of less common syndromes that can also confer hereditary cancer risk.^{4,7,21,42-45} Numerous recent studies have shown that panel testing can significantly increase the rate of detection of pathogenic variants, with the most frequently identified pathogenic variants (outside of BRCA1 and BRCA2) being in PALB2, CHEK2, and ATM.^{4,21,44} As noted above, there is a

comparatively limited understanding of individual breast cancer risk associated with mutations in genes other than BRCA1 and BRCA2. However, the presence of mutations in PALB2, ATM, truncating mutations in CHEK2, and possibly other genes are likely to be associated with lifetime breast cancer risks of greater than 20% and therefore, in the United States, at least support a decision for enhanced surveillance with annual mammography with tomosynthesis and breast MRI with contrast. Mutations in other genes may also reach this threshold, although the rarity of such mutations and the possibility of subtype-specific predisposition make risk estimation more challenging. A multi-gene panel may include genes with varying degrees of evidentiary support and “actionability.” This testing method is optimal when the individual genes included are clinically valid and comprehensively address the details of each patient's case.

Panel testing can be considered for patients who qualify for hereditary breast cancer testing to more efficiently and cost-effectively evaluate genes that confer risk and impact management recommendations. When genetic testing is being recommended based on phenotypic syndromes (for example three or more close family members affected by breast cancer at any age) then multi-gene panel testing is likely to be more efficient in evaluating patients. In fact, the most recent NCCN guidelines allow that panel testing will largely replace sequential gene sequencing (i.e., the older approach of evaluating BRCA pathogenic variants first, then selecting additional genes if BRCA tests are negative).^{20,28,41} Insurance companies are urged to incorporate the advantages of panel testing into their algorithms to allow hereditary cancer syndrome testing for patients at high risk. Surgeons, genetic counselors, and other health care professionals who order panel testing for breast cancer patients or their family members should at a minimum test the breast cancer genes that are clinically actionable given the current state of medical evidence. Testing of additional genes can also be performed at the discretion of the ordering physician or as directed by the family history.

Variant of uncertain significance (VUS)

Variants of uncertain significance are DNA sequences that are NOT clinically actionable. This type of result needs to be considered as inconclusive. For example, a patient who receives a genetic testing result of “BRCA1 variant of uncertain significance” should NOT be recommended for a change in management based on that test result alone. No clinical treatment plan or risk management plan should be influenced by a VUS. These are DNA sequences about which the lab is still accruing data for definitive classification as to benign or pathogenic. The vast majority are re-classified as benign when enough data are collected. Usually it takes several years for the reclassification to take place.^{42,46}

The American College of Medical Genetics has published guidelines for reporting DNA sequence variations.⁴⁷ The rate of identifying VUSs can be high when new syndromes are identified but that rate decreases as data regarding those genes and the VUSs are accrued. Current rates of identifying a VUS with newer multi-gene panel testing is reported to be between 6.7-41.7%.^{21,42-44} There are still VUSs identified with BRCA1/2 testing. However, the rates are generally much lower, ranging from 2-5%, now that testing of these two syndromes has been available for more than 20 years. In general, patients with VUSs should be managed

based on their family history, medical history, age, and other factors that influence breast cancer risk. No weight should be given to the VUS found, and co-segregation among affected family members is not conclusive evidence of pathogenicity.

This statement was developed by the panel members listed below, and on February 10, 2019, was approved by the Board of Directors.

Panel:

- Chair, Eric R. Manahan, MD, MBA, FACS, Hamilton Medical Center, Dalton, GA
- Molly Sebastian, MD, FACS, Medical Director, Reinsch Pierce Family Center for Breast Health, Virginia Hospital Center, Arlington, VA – nothing to disclose
- Kevin S. Hughes, M.D., FACS, Professor of Surgery, Harvard Medical School, Co-Director, Avon Comprehensive Breast Evaluation Center Massachusetts General Hospital, Boston, MA
- Judy C. Boughey, M.D., FACS, Professor of Surgery, Mayo Clinic, Rochester MN
- Henry M. Kuerer, M.D., FACS, Endowed Distinguished Professor of Surgery and Cancer Research, Executive Director Breast Programs, MD Anderson Cancer Network; University of Texas MD Anderson Cancer Center, Houston, TX
- David M. Euhus, MD, FACS, Professor of Surgery, Johns Hopkins Hospital, Baltimore, MD
- Mark E. Robson, MD, Chief, Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY
- Susan K. Boolbol, MD, Chief of Breast Surgery, Mount Sinai Beth Israel, New York, NY
- Banu K. Arun, MD, University of Texas MD Anderson Cancer Center, Houston, TX
- Walton A. Taylor, MD, FACS, Texas Health Physicians Group, Dallas, TX

Relevant Author Disclosures

Kevin Hughes- Honoraria from Focal Therapeutics (Surgical implant for radiation planning with breast conservation), 23andMe, and is a founder of and has a financial interest in CRA Health (Formerly Hughes RiskApps). Dr. Hughes's interests were reviewed and are managed by Massachusetts General Hospital and Partners Health Care in accordance with their conflict of interest policies.

Mark Robson- Honoraria (Advisory): AstraZeneca,
Consulting or Advisory: McKesson, AstraZeneca, Merck (uncompensated)
Research Funding: AstraZeneca (Institution), Myriad (Institution, in-kind), Invitae (Institution, in-kind), AbbVie (institution), Tesaro (institution), Medivation (Institution)
Travel, Accommodation, Expenses: AstraZeneca

Banu Arun- Research Funding: AstraZeneca (Institution), Invitae (Institution), AbbVie (Institution), PharmaMar (Institution)

- References -

1. Plichta, J, Sebastian, M, Hughes, K, et al. Germline genetic testing: What the breast surgeon needs to know. *Ann of Surg Oncol.* (accepted for publication 2019).
2. National Cancer Institute. Cancer Stat Fact Sheets. <http://seer.cancer.gov/> Accessed January 10, 2019.
3. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature.* 2012;490:61-70.
4. Castera L, Krieger S, Rousselin A, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet.* 2014;22:1305-1313.
5. Walsh T, Lee MK, Casadei S, et al. Detection of inherited pathogenic variants for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci USA.* 2010;107:12629-12633.
6. van der Groep P, van der Wall E, van Diest PJ. Pathology of hereditary breast cancer. *Cell Oncol (Dordr).* 2011;34:71-88.
7. Walsh T, King MC. Ten genes for inherited breast cancer. *Cancer Cell.* 2007;11:103-105.
8. Meindl A, Ditsch N, Kast K, Schmutzler RK. Hereditary breast and ovarian cancer: New genes, new treatments, new concepts. *Dtsch Arztebl Int.* 2011;108:323-330.
9. National Research Genome Institute (NIH). Learning about the BRCAx study. <http://www.genome.gov/10000532> Accessed January 10, 2019.
10. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 pathogenic variant carriers with cancer risk and mortality. *JAMA.* 2010;304:967-975.
11. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 pathogenic variant. *N Engl J Med.* 2002;346:1609-1615.
12. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene pathogenic variant carriers. *J Natl Cancer Inst.* 2001;93:1633-1637.
13. Kurian AW, Sigal BM, Plevrittis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 pathogenic variant carriers. *J Clin Oncol.* 2010;28:222-231.
14. Narod SA, Offit K. Prevention and management of hereditary breast cancer. *J Clin Oncol.* 2005;23:1656-1663.
15. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 pathogenic variant carriers: international case-control study. *J Clin Oncol.* 2005;23:7491-7496.
16. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 pathogenic variant carriers: a case-control study. *Lancet.* 2000;356:1876-1881.
17. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 pathogenic variants. *N Engl J Med.* 2002;346:1616-1622.
18. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 pathogenic variant carriers: The PROSE Study Group. *J Clin Oncol.* 2004;22:1055-1062.
19. Beitsch PD, Whitworth PW, Hughes K, et al. Underdiagnosis of hereditary breast cancer: Are genetic testing guidelines a tool or an obstacle? *J Clin Oncol.* 2018;37:1-8.
20. Yang S, Axilbund JE, O'Leary E, et al. Underdiagnosis of hereditary breast and ovarian cancer in Medicare patients: Genetic testing criteria miss the mark. *Ann Surg Oncol.* 2018;25:2925-2931.
21. Kapoor NS, Curcio LD, Blakemore CA, et al. Multigene panel testing detects equal rates of pathogenic BRCA1/2 pathogenic variants and has a higher diagnostic yield compared to limited BRCA1/2 analysis alone in patients at risk for hereditary breast cancer. *Ann Surg Oncol.* 2015;22:3282-3288.
22. Domchek, SM, Bradbury A, Garber JE, Offit K, Robson ME. Multiplex genetic testing for cancer susceptibility: Out on the high wire without a net? *J Clin Oncol.* 2013;31:1267-1270.
23. Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J Clin Oncol.* 2005; 23:276-292.
24. Pierce LJ, Haffty BG. Radiotherapy in the treatment of hereditary breast cancer. *Semin Radiat Oncol.* 2011;21:43-50.
25. Sikov WM. Assessing the role of platinum agents in aggressive breast cancers. *Curr Oncol Rep.* 2015;17:3.
26. Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: Current data and future prospects. *BMC Med.* 2015;13:188.
27. Hughes KS, Parmigiani G, Braun DP. All syndromes known to man evaluator. 2018; <https://www.ask2me.org/>. Accessed August 13, 2018.
28. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 pathogenic variants detected in case series unselected for family history: A combined analysis of 22 studies. *Am J Hum Genet.* 2003;72:1117-1130.
29. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. *Cancer.* 1996;77:2318-2324.
30. Schmidt MK, Hogervorst F, van Hien R, et al. Age- and tumor subtype-specific breast cancer risk estimates for CHEK2*1100delC carriers. *J Clin Oncol.* 2016;34(23):2750-2760.
31. Milne RL. Variants in the ATM gene and breast cancer susceptibility. *Genome Med.* 2009;1(1):12.
32. Stanford Medicine Cancer Institute. Decision tool for women with BRCA pathogenic variants.

- <http://brcatool.stanford.edu/brca.html> Accessed January 2019.
33. American College of Surgeons. Cancer. <http://www.facs.org/cancerprogram/index.html> Accessed January 10, 2019.
 34. Nelson HD, Fu R, Goddard K, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: Systematic review to update the U.S. Preventive Services Task Force Recommendation. Evidence Syntheses, No. 101. 2013. <http://www.ncbi.nlm.nih.gov/books/NBK179201/> Accessed January 10, 2019.
 35. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
 36. Nelson H, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: A systematic review to update the U.S. Preventive Services Task Force recommendation. *Ann Intern Med.* 2014;160:255-266.
 37. Rainville IR, Rana HQ. Next-generation sequencing for inherited breast cancer risk: Counseling through the complexity. *Curr Oncol Rep.* 2014;16:371.
 38. Ku CS, Cooper DN, Iacopetta B, et al. Integrating next generation sequencing into the diagnostic testing of inherited cancer predisposition. *Clin Genet.* 2013; 83:2-6.
 39. Simen B, Yin L, Goswami C, et al. Validation of a next-generation-sequencing cancer panel for use in the clinical laboratory. *Arch Pathol Lab Med.* 2015;139:508-517.
 40. Association for Molecular Pathology v Myriad Genetics, Inc., 569 US (2013).
 41. Azvolinsky A. Supreme Court ruling broadens BRCA testing options. *J Natl Cancer Inst.* 2013;105:1671-1672.
 42. LaDuca H, Stuenkel AJ, Dolinsky JS, et al. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genet Med.* 2014;16:830-837.
 43. Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol.* 2014;32:2001-2009.
 44. Tung N, Battelli C, Allen B, et al. Frequency of pathogenic variants in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer.* 2015;121:25-33.
 45. Yorczyk A, Robinson LS, Ross TS. Use of panel tests in place of single gene tests in the cancer genetics clinic. *Clin Genet.* 2015;88:278-282.
 46. King MC, Levy-Lahad E, Lahad A. Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award. *JAMA.* 2014;312:1091-1092.
 47. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405-424.