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Executive Summary

Executive Summary of the Early-Onset Breast Cancer Evidence Review Conference

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The Centers for Disease Control and Prevention launched the Bring Your Brave campaign to increase knowledge about early-onset breast cancer, defined as breast cancer in women aged 18–45 years. The American College of Obstetricians and Gynecologists convened a panel of experts in breast disease from the Society for Academic Specialists in General Obstetrics and Gynecology to review relevant literature, validated tools, best practices, and practice guidelines as a first step toward developing educational materials for women's health care providers about early-onset breast cancer. Panel members conducted structured literature reviews, which were then reviewed by other panel members and discussed at an in-person meeting of stakeholder professional and patient advocacy organizations in April 2019. This article summarizes the relevant literature, existing guidance, and validated tools to guide health care providers in the prevention, early detection, and special considerations of early-onset breast cancer. Substantive knowledge gaps were noted and summarized to provide guidance for future research.

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Early-onset breast cancer is breast cancer occurring in women aged 18–45 years. From 2012 to 2016, early-onset breast cancer accounted for 10.3% of all new female breast cancer cases. Furthermore, 5.6% of breast cancer deaths in the United States occur in women younger than 45 years.[1] Approximately 15% of breast cancer deaths result from breast cancers initially diagnosed before age 45 years.[2] Because of the

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Participation in this project as an attendee of the Evidence Review Conference does not constitute organizational or individual endorsement of the conclusions. Information in this article should not be construed as the official position or policy of, or should any endorsements be inferred by CDC, HHS, or the U.S. Government.

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

David Chelmow is the President of the Council of University Chairs of Obstetrics and Gynecology, the Treasurer of ASCCP, the Editor-in-Chief of the Medscape Obstetrics and Gynecology Clinical Reference Book, and is on the American Board of Obstetrics and Gynecology Board of Directors. Mark Pearlman is a member of the Planned Parenthood Federation of America's National Medical Committee, a member of the National Comprehensive Cancer Network Committee on Breast Cancer Screening and Diagnosis, and a Contributing Editor for OBG Management. Amy Young is the President of the Society for Academic Specialists in General Obstetrics and Gynecology. Mallory Kremer is a consultant for March of Dimes California's Preterm Birth Toolkit. Julia O'Hara is an employee of the American College of Obstetricians and Gynecologists. The other authors did not report any potential conflicts of interest.

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Table 1. Early-Onset Breast Cancer Evidence Review Conference Attendees

Attendee Role	Attendee Name(s)
Evidence review panelist	David Chelmow, MD (Chair)
	Amy Young, MD
	Dana Scott, MD
	Laura Bozzuto, MD
	Mallory Kremer, MD
	Mark Pearlman, MD
	Myrlene Jeudy, MD
	Sandra Dayaratna, MD
Stakeholder organization representative	Allison W. Kurian, MD, MSc (National Comprehensive Cancer Network)
	Amy L. Davis, DO, MS, FACP, FAAHPM (American College of Physicians)
	Andrea Forman, MS, LCGC (National Society of Genetic Counselors)
	Dana Smetherman, MD, MPH, MBA, FCAR (American College of Radiology)
	Deborah Lindner, MD, FACOG (Bright Pink)
	Edith P. Mitchell, MD, MACP, FCPP (National Medical Association)
	Karen Smith, MD, MPH (American Society of Clinical Oncology)
	Meredith Browne, PA-C (Association of Physician Assistants in Obstetrics and Gynecology)
	Mike Walsh, MD (American College of Medical Genetics)
	Nancy Lee, MD (Black Women's Health Imperative)
	Robert Smith, PhD (American Cancer Society)
	Rachel Gorham, MSN, WHNP-DC, AGN-BC (Nurse Practitioners in Women's Health)
	Sarah Coles, MD (American Academy of Family Physicians)
ACOG staff	Christopher M. Zahn, MD
	Emily Greenwood
	Julia S. O'Hara, MPH
	Nancy O'Reilly, MHS
CDC representative and cooperative agreement technical monitor	Temeika Fairley, PhD
Consultant	Dana Trevas (Shea & Trevas, Inc.)
Observer	Christina R. Lachance, MPH (Health Resources Services Administration Office of Women's Health ex-officio to the CDC Advisory Committee on Breast Cancer in Young Women)
	Roshni Devchand, MPH (Hager Sharp)

ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention.

young age of onset, women with early-onset breast cancer have special survivorship issues, including contraception, management of menopausal symptoms, fertility conservation, and pregnancy. The Centers for Disease Control and Prevention (CDC) sponsored development of educational material on early-onset breast cancer. The educational material geared towards patients, Bring Your Brave, is available on the CDC website (https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/index.htm). The CDC awarded the American College of Obstetricians and Gynecologists (ACOG) a grant to develop accompanying health care provider material, available on line at www.acog.org/eobc.

METHODS

The American College of Obstetricians and Gynecologists convened an expert panel to identify the best evidence and practices from the literature, existing relevant society guidelines, and available validated specific or generalizable clinical tools. The panel was recruited from the Society for Academic Specialists in General Obstetrics and Gynecology to review and summarize the evidence. Panel members were required to have expertise in evidence review and synthesis. Subspecialty expertise in breast disease was also sought. Several of the panel members had completed subspecialty fellowship training in breast disease. The panel developed 10 separate research questions and used the PICO criteria (P=patient, problem, or population; I=intervention; C=comparison, control, or comparator; O=outcome[s]) to frame the literature review. These questions form the organizing basis for this executive summary.

Experts in literature searches from the ACOG Resource Center searched the Cochrane Library,

MEDLINE through Ovid, and PubMed for references not indexed through MEDLINE from January 2010 to January 2019. Literature was organized by level of evidence. Published guidelines were categorized separately from references. A primary reviewer was assigned to each topic to review titles and abstracts, then the entire manuscript when appropriate. Panel members expanded the search criteria when necessary, either increasing the timeframe or broadening the search to other populations, particularly when inadequate evidence was found on the 18–45 years age group. Reference lists from papers found in the search were also reviewed. Internet searches with standard search engines were performed to seek guidelines, recommendations, and tools that might not have been published in peer-reviewed publications. Relevant information was compiled into an evidence summary template. Completed templates were then reviewed by a secondary reviewer and the primary and secondary reviewer worked together on revisions in response to the secondary reviewer's comments.

The American College of Obstetricians and Gynecologists convened the Early-Onset Breast Cancer Evidence Review Conference in Washington, DC, April 1–2, 2019, including the panel members and representatives from stakeholder professional and patient advocacy organizations (Table 1). Panel members presented their reviews to the convened group, which discussed each section. Comments from the discussion were integrated into the review summary by the primary reviewer. The revised summaries were sent to a tertiary reviewer for final review, and final revisions were made by the primary reviewer. The final reviews (see Appendices 1–10) were used to develop the educational material.

EPIDEMIOLOGY, DEMOGRAPHICS, AND SURVIVAL

Breast cancer is the most common form of cancer in women and represents the second leading cause of cancer death in women.[3] National Cancer Institute data from 2012 to 2016 indicated that 1.9% of new breast cancer cases and 0.9% of cancer deaths occurred among women aged 20–34 years, and 8.4% of new breast cancer cases and 4.7% of breast cancer deaths occurred among women aged 35–44 years. Black women had the highest death rate at 28.1 per 100,000 persons. Although 5-year relative survival rates were largely similar across age groups, women younger than age 45 years had among the lowest rates, second only to women aged 75 years and older.[1,4] See Table 1 in Appendix 1, available online at http://links.lww.com/AOG/B864, for breast cancer incidence rates by age and race. See Table 2 in Appendix 1 (http://links.lww.com/AOG/B864) for breast cancer mortality rates by age and race.

Younger women tend to have more aggressive and biologically unfavorable tumor subtypes than older women and poorer survival in early stage disease (stages I and II) when compared with women older than 40 years. In advanced stages, younger women have lower mortality, likely because of overall general health.[5] Although mortality trends have improved in all women, young black women continue to have higher mortality rates than other young women with breast cancer, irrespective of stage or hormone receptors. Annual hazard rates of death of young black women are improving more slowly than other races and ethnicities, suggesting less benefit from advances in treatment. Poorer prognosis in black women is thought to result from multiple factors, including more aggressive tumors, access barriers, and social determinants of health[6] (see Appendix 1 [http://links.lww.com/AOG/B864] for complete evidence summary).

GENETIC RISK FACTORS

Cancer genes such as autosomal dominant single gene pathogenic variants account for approximately 5–10% of all cases of breast cancer. The *BRCA1* and *BRCA2* genes are the most common, representing more than 50% of all genes associated with early-onset breast cancer. Women who carry pathogenic variants have an increased lifetime risk of breast and other cancers and are at higher risk of developing early-onset breast cancer. *BRCA* pathogenic variants occur more frequently in certain populations (Table 2), most notably in persons of Ashkenazi Jewish descent. The prevalence of *BRCA1* and *BRCA2* pathogenic variants is 1 in 40 (2.5%) in Ashkenazi Jews, compared with the general population prevalence of 1 in 400–600.[7,8] In Ashkenazi Jews, three site-specific founder mutations have been identified (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*), representing more than 90% of the *BRCA* mutations.

In the United States, African American women have a lower incidence of breast cancer than Caucasian women, but higher breast cancer mortality rates.[9] The higher mortality rate seems to be associated with two patterns: proportionally more African American women are diagnosed before 50 years of age (30–40% of all breast cancers in African American women) compared with Caucasian women (approximately 20% of all breast cancer in Caucasian women), and African American women have a twofold higher rate

Table 2. Likelihood of Carrying a *BRCA* Pathogenic Variant in Women With Breast Cancer

Race and Ethnicity	*BRCA1*	*BRCA2*
Caucasian	2–3%	2%
African American	1%	3%
Hispanic	4%	No data
Asian American	Less than 1%	No data
Ashkenazi Jewish	8–10%	1%

Data from Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35–64 years. Cancer Res 2006;66:8297–308 *and* John EM, Miron A, Gong G, Phipps AI, Felberg A, Li FP, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 2007;298:2869–76.

of breast cancers that lack expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, known as triple-negative cancer.[10] Triple-negative tumors are biologically more active, with higher recurrence and mortality rates compared with most other breast cancer phenotypes.[10,11] These differences do not appear to be due to higher carriage rates of single gene mutations such as *BRCA1* and *BRCA2* alone.

Currently, population-based screening for *BRCA* genes in the absence of other risk factors is not broadly recommended, given their rarity and the uncertain benefit of large-scale testing.[12] Because Ashkenazi Jews have a 10-fold increased risk of carrying a founder mutation in *BRCA1* or *BRCA2*, consensus guidelines recommend offering routine testing for the three specific mutations.[12,13]

The National Comprehensive Cancer Network, ACOG, the U.S. Preventive Services Task Force, the American Society of Breast Surgeons, and the American College of Medical Genetics provide recommendations for risk assessment, referral to genetic counseling or offering of genetic testing based on risk identification, and management of men and women identified with a genetic predisposition for early-onset breast cancer (see Table 2 in Appendix 2, available online at http://links.lww.com/AOG/B865). Common factors considered in risk assessment include the following:

1. Personal history of breast, ovarian, tubal, pancreatic, prostate, and other cancers and either early age of onset of these cancers or other cancer-specific factors that increase the likelihood of carrying a pathogenic variant in a breast cancer gene (eg, triple-negative tumors).
2. Family history of breast, ovarian, tubal, pancreatic, prostate, and other cancers suggesting an autosomal dominant pattern of inheritance.

In addition to *BRCA1* and *BRCA2*, other important but less common autosomal dominant genes are associated with early-onset breast cancer risk. Panel testing has emerged in the past few years to assess for possible gene alterations that have been implicated in early-onset breast cancer. The specific panels are usually defined by the laboratory offering the testing. A woman identified with a pathogenic variant placing her at increased risk for early-onset breast cancer can undergo increased surveillance to detect breast cancer at earlier stages, risk-reduction surgery, or chemoprophylaxis.[13] Depending on the gene, surveillance may start at an earlier age and include mammography, magnetic resonance imaging (MRI), or both. The natural history of early-onset breast cancer is fairly well understood for some genes (eg, BRCA), but there is less complete understanding of the penetrance and age of onset for those with non-*BRCA* genes associated with breast cancer. Table 3 provides an overview of common genes included in panel testing, along with recommendations for surveillance and risk reduction (see Appendix 2 [http://links.lww.com/AOG/B865] for complete evidence summary).

FAMILY HISTORY OF EARLY-ONSET BREAST CANCER

Assessment of family history is essential when evaluating young women accessing primary care. Understanding a woman's family history of breast cancer can identify individuals at elevated risk for hereditary breast cancer or women who would benefit from increased breast cancer surveillance. The American College of Obstetricians and Gynecologists, the Society of Gynecologic Oncologists, the U.S. Preventive Services Task Force, the National Institute of Health Care Excellence, and the National Comprehensive Cancer Network have published guidelines recommending assessment of family history and screening for patients at increased risk of breast cancer. The American College of Obstetricians and Gynecologists states that screening should include at minimum a personal cancer history and first- and second-degree relatives' cancer history that includes a description of the type of primary cancer, the age of onset, and the lineage of the family member.[14] The National Comprehensive Cancer Network clinical guidelines recommend genetic assessment for all patients with first- and second-degree relatives diagnosed with breast cancer younger than age 50 years.[13] The U.S. Preventive Services Task Force recommends screening of women who have family members with breast, ovarian, tubal, or peritoneal cancer using one of several screening tools designed to identify a family

Table 3. Management of Women With Breast-Cancer–Associated Genes*

	Screening Recommendation†			Risk Reduction	
Gene	CBE‡	Mammography	MRI	Chemoprophylaxis With Tamoxifen	RRM
BRCA1	Start: Age 25 years	Start: Age 30 years	Start: Age 25 years	Limited data to support tamoxifen.‖	Discuss option of RRM.¶
	Frequency: Every 6–12 mo	Frequency: Annual§	Frequency: Annual§		
BRCA2	Start: Age 25 years	Start: Age 30 years	Start: Age 25 years	Limited data to support tamoxifen.‖	Discuss option of RRM.¶
	Frequency: Every 6–12 months	Frequency: Annual§	Frequency: Annual§		
ATM	No recommendations provided	Start: Age 40 years	Consider start: Age 40 years	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.
		Frequency: Annual	Frequency: Annual		
CHEK2	No recommendations provided	Start: Age 40 years	Consider start: 40 years	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.
		Frequency: Annual	Frequency: Annual		
PALB2	No recommendations provided	Start: Age 30 years	Consider start: 30 years	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.‖
		Frequency: Annual	Frequency: Annual		
PTEN	Start: Age 25 years	Start: Age 30 years	Start: Age 30 years	Insufficient data to address efficacy of chemoprophylaxis.	Discuss option of RRM.‖
	Frequency: Every 6–12 months	Frequency: Annual§	Frequency: Annual§		
STK11	Start: Age ~25 years	Start: Age ~25 years	Start: Age 25 years	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history‖
	Frequency: Every 6 months#	Frequency: Annual#	Frequency: Annual#		
NF1	No recommendations provided	Start: Age 30 years	Consider from 30–50 years	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.
		Frequency: Annual	Frequency: Annual		
NBN	No recommendations provided	Start: Age 40 years	Consider Start: Age 40 years	Insufficient data to address efficacy of chemoprophylaxis.	No data on the benefit of RRM, but may be considered based on family history.
		Frequency: Annual	Frequency: Annual		

(*continued*)

Table 3. Management of Women With Breast-Cancer–Associated Genes[*] (*continued*)

	Screening Recommendation[†]			Risk Reduction	
Gene	CBE[‡]	Mammography	MRI	Chemoprophylaxis With Tamoxifen	RRM
TP53 (P53)	Start: Age 20 years[‡]	Start: Age 30 years	Start: Age 20 years or earlier if family history of younger-onset breast cancer Frequency: Annual[§]	Insufficient data to address efficacy of chemoprophylaxis.	Discuss option of RRM.[¶]
	Frequency: Every 6–12 months	Frequency: Annual[§]			
CDH1	No recommendations provided	Start: Age 30 years	Consider start: Age 30 years	Insufficient data to address efficacy of chemoprophylaxis.	Discuss option of RRM (no data on benefit).[¶]
		Frequency: Annual	Frequency: Annual		

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[*] CBE, clinical breast examination; MRI, magnetic resonance imaging; RRM, risk reduction mastectomy.

[†] The age for starting breast screening may be earlier depending on earliest age of diagnosis in the family (if before age 30 years).

[‡] Self-breast awareness (also called breast awareness) is recommended. It is defined as women being familiar with their breasts so they can promptly report any changes to their health care provider.

[§] Mammography and MRI are recommended to age 75; breast imaging beyond that age should be individualized.

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[¶] Mastectomy counseling includes degree of protection, reconstruction options, and risks of procedures.

[#] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal V.2.2019. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 12, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing.[12] Genetic counselors can help determine which of the many available panels of genetic testing are most appropriate and cost-effective.

Women with deleterious genetic mutations tend to present with breast cancer at an earlier age. However, some studies suggest that women with a positive family history and no known genetic mutation are at increased risk of developing breast cancer and these cancers occur at an earlier age compared with those in the general population who did not have a known mutation.[15–17] The Nurses' Health Study and a systematic review and meta-analysis by Pharoah et al identified consistent findings.[18,19] In the Nurses' Health Study, women with a family member diagnosed with breast cancer before age 50 years had an increased risk for breast cancer compared with women of the same age who had family members diagnosed at older ages. Compared with women with no family history, those whose mother was diagnosed before age 50 years had an adjusted relative risk (RR) of 1.69 (95% CI 1.39–2.05), and those whose mother was diagnosed at 50 or older had an RR of 1.37 (95% CI 1.22–1.53).[18] Pharaoh et al found that a history of breast cancer in at least one first-degree relative resulted in RR estimates ranging from 1.2 to 8.8, with most studies showing RRs between 2 and 3.[19] The pooled risk estimate for having two affected first-degree relatives was 3.6 (95% CI 2.5–5.0).[19] Genetic mutations were not factored out in many of the older studies.

There are limited data on outcomes for women with an elevated risk of breast cancer by family history without an established familial genetic mutation. National guidelines consistently emphasize the importance of gathering a thorough family history of breast cancer. However, these guidelines are based on limited data estimating lifetime and age-based breast

cancer risk for women in families that do not have identified genetic mutation carriers. Many of the current guidelines are based on expert opinion and studies of family history that were published before the availability of genetic testing for mutations such as *BRCA1* and *BRCA2*.

There is general consensus that women with a lifetime risk of breast cancer greater than 20%, as determined by any model, are at high risk. Multiple validated models can be used to determine the probability of a genetic mutation, which increases the risk of breast cancer. There is no consensus and there are no data to support the recommendation of one model over another.[20] Currently, the National Comprehensive Cancer Network recommends that women with an estimated lifetime risk of breast cancer of 20% or higher, determined by models largely based on family history (eg, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, Claus, BRCAPRO, or Tyrer-Cuzick) should be offered annual mammography screening starting at age 30 years and annual breast screening by MRI starting at age 25 years[13,21] (see Appendix 3, available online at http://links.lww.com/AOG/B866, for complete evidence summary). This is in contrast to screening recommendations for average risk women, which all recommend screening with mammography alone, starting at age 40–50 years, depending on the source.[14]

UNDERSTANDING GENETIC COUNSELING AND TESTING

There are at least moderate-quality data that risk assessment, referral for genetic counseling, and genetic testing provide net benefit in women at high risk for early-onset breast cancer. These steps can form the basis for intensive surveillance for early detection or use of risk-reduction methods that have proven effective in detecting breast cancer at an earlier stage and decreasing mortality rates.[12]

The National Institutes of Health maintains a periodically updated list of online resources designed to educate and assist health care providers on various topics ranging from basic genetics, understanding risk assessment, criteria for referral to genetic counseling, and interpretation of genetic test results.[22] Other national societies have created genetics "toolkits" or published guidance to educate health care providers on basic cancer genetics, risk assessment, and referral recommendations[23,24] (see Table 1 in Appendix 4, available online at http://links.lww.com/AOG/B867, for a list of useful websites).

Providers can also learn about these topics through other mechanisms, such as continuing medical education and online learning. The depth and detail of the material covered range from superficial (eg, short "expert" videos) to online courses that take place over several months. Very few online courses provide a validated assessment of competency or certification. The content of specific training and assessment of competency for physicians who counsel patients about genetic testing have not been standardized.

The U.S. Preventive Services Task Force concluded that health care providers should assess risk based on personal or family history and refer women who screen positive to cancer genetic counselors.[12] A number of validated tools exist to determine who should be referred for genetic testing,[25–29] and several professional specialty societies have developed lists of indications for referral and testing.[13,14,30] These tools are specifically designed to evaluate who should be referred for *BRCA* testing; however, because *BRCA* carriers represent the greatest proportion of women at genetic risk for early-onset breast cancer, these tools are reasonable proxies for genetic screening for early-onset breast cancer. These tools have been validated in some populations (non-Hispanic white women), and it is not known how the tools perform in nonwhite populations. It remains unclear how frequently these tools are used in practice by physicians. Evaluation suggests that the tools miss a substantial proportion of carriers.[31,32] Interpretation of genetic test results can be complex and usually requires a qualified individual who has specific training in cancer genetics.[12,33,34]

A number of tools and calculators are used to estimate lifetime invasive breast cancer risk, but not necessarily the predicted age of onset (See Table 2 in Appendix 4, http://links.lww.com/AOG/B867, for a comparison of four commonly used risk-assessment models: Tyrer-Cuzick, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, Claus, and the modified Gail model, also called the Breast Cancer Risk Assessment Tool).

Numerous national consensus guidelines and recommendations have been developed to assist health care providers in communicating with patients about referral to genetic counseling or testing for early-onset breast cancer genes or both.[13,14,30] Some specialty societies have produced separate guidance specifically addressing both the interpretation of genetic test results and how to communicate these results to patients.[33] Some guidelines are frequently updated,[13] whereas others are periodically revised (ie, every few years),[12,14,30] resulting in guidance that

may differ, causing confusion among health care providers and patients. All current guidelines recommend that women should be screened for personal and family history of breast and other related cancers and referred for genetic counseling or testing or both as appropriate. In addition, all guidelines recommend that determination for testing and pretest and posttest counseling should be performed by individuals with appropriate training. However, there is a shortage of genetic counselors in the United States, which has been identified as a barrier to effective counseling[35,36] (see Appendix 4 [http://links.lww.com/AOG/B867] for complete evidence summary).

DENSE BREASTS AND THE RISK OF EARLY-ONSET BREAST CANCER

Breast tissue is comprised of fibroglandular tissue and fat. The fibroglandular tissue is a mixture of fibrous stroma and ductal epithelium and appears denser or brighter on mammography because the X-rays are not able to penetrate at the same rate as fatty tissue. The Breast Imaging-Reporting and Data System for mammography developed by the American College of Radiology includes a subjective assessment of how much fibroglandular tissue is present (see Table 1 in Appendix 5, available online at http://links.lww.com/AOG/B868). As women age, breast tissue typically becomes less dense. Most of the data about breast density and cancer risk come from women older than age 50 years. Dense breasts are present in the majority of younger women.

A systematic review of risk for breast cancer in women aged 40–49 years reported that extremely dense breasts were associated with an increased risk of breast cancer when compared with breasts with scattered fibroglandular densities (RR 2.04, 95% CI 1.84–2.26).[37] In a more recent case-control study of 213 Korean women with breast cancer, women who had the highest breast density, described as 50% density or higher, after adjusting for multiple variable, had an adjusted odds ratio of 2.98 (95% CI 0.99–9.03) for breast cancer. The wide CIs in this nonsignificant finding is likely related to the small numbers of included women and future studies should be monitored. Median age in the study was 51.5 years, with 45% of cancers diagnosed before age 50 years.[38] Older studies are harder to interpret because they used many different ways of characterizing breast density, but in general, when comparing the most dense with the least dense group, there appears to be an increased risk of breast cancer, with RRs as high as 4.64 (95% CI 3.64–5.91) reported.[39] As the majority of premenopausal women have dense breasts, it is not clear that RRs estimated from comparisons of extremes of breast density categories are appropriate measures of risk in this age group.

Dense breasts decrease the sensitivity of mammography because dense breast tissue appears radiopaque, similar to breast cancers, decreasing visual contrast ("masking"). In women with extremely dense breasts, mammography has 62% sensitivity for detection of breast cancer, compared with 88% sensitivity for women with fatty breasts.[40] One way to assess delay in diagnosis is to determine the rate of interval cancers, those cancers found between recommended screening intervals after a normal mammogram. No studies evaluating masking due to breast density have exclusively evaluated women with early-onset breast cancer. Most studies included large proportions of women older than age 50 years, though women aged 40–49 years were included. More recent evidence suggests that dense breasts appear to be associated with at least a twofold increased risk of interval cancers as well as a worse prognosis, including larger tumor size and more node-positive disease.[41–43]

Studies of adjunctive screening of women with dense breasts with ultrasonography and MRI generally noted higher cancer detection rates and earlier diagnoses, but also showed increase in biopsy for benign lesions and increased healthcare costs, and no study showed improvement in mortality (see Appendix 5 [http://links.lww.com/AOG/B868] for complete evidence summary). The majority of women under age 46 years have dense breasts, so any recommendations for additional screening in this age group would require additional testing in a large number of women whose baseline risk is low.

Most organizations, including ACOG and the U.S. Preventive Services Task Force, do not recommend additional screening in women younger than age 46 years with a normal mammogram and dense breasts. The Society of Breast Imaging expresses concern for a delay in diagnosis and later stage at diagnosis of noncalcified breast cancers because of dense breast tissue and suggests that ultrasonography may be of benefit, provided the woman is willing to accept an increased risk of false-positive results.[44] The National Comprehensive Cancer Network recommends that women with mammographically dense breast tissue (heterogeneously or extremely dense tissue) be counseled about the risks and benefits of supplemental screening.[45] Neither of these organizations specifically address dense breasts in younger women.

Mandatory breast density reporting has been enacted as legislation in an increasing number of states. Many patients receive letters notifying them of their breast density, and interpretation of these letters

can be challenging for patients and health care providers. In early 2019, Congress authorized the U.S. Food and Drug Administration to amend the Mammography Quality Standards Act of 1992 to include mandatory breast density reporting at the federal level. The public comment period for the proposed changes to the legislation ended in June 2019, and final regulations should be forthcoming. The American College of Obstetricians and Gynecologists recommends that health care providers comply with state laws that require disclosure of breast density in mammogram reports.[46]

Younger women with dense breasts and no other risk factors can be counseled that dense breasts are very common in this age group, and supplemental screening methods are available. However, they are not specifically recommended, have significant risk of false positives, and have not been shown to change outcome. When mammographic density in combination with other risk factors places the woman at above-average risk, additional screening with ultrasonography may be warranted and a shared decision-making model can be applied. Some breast cancer risk calculators integrate breast density and can be used to assess overall risk in these women (see Appendix 5 [http://links.lww.com/AOG/B868] for complete evidence summary).

EFFECT OF HEALTH HISTORY ON EARLY-ONSET BREAST CANCER

History of Proliferative Breast Disease

Many proliferative breast diseases increase the risk of breast cancer, but the effect on early-onset breast cancer risk is unknown. Atypical ductal hyperplasia carries a more than 20% risk of ductal carcinoma in situ (DCIS) or invasive malignancy at the time of diagnosis, so it is typically excised.[47] Both atypical ductal hyperplasia and atypical lobular hyperplasia are associated with a fourfold increased lifetime risk of breast cancer.[47–49] When atypical lobular hyperplasia is an incidental finding and there is concordance between radiologic and pathologic findings regarding the targeted biopsied lesion, it is less likely to be associated with a concurrent malignancy, so close monitoring is usually appropriate.[48] Lobular carcinoma in situ is not considered a preinvasive malignancy like DCIS, but does significantly increase the lifetime risk of breast cancer (RR 6.9–11, absolute risk 7.1% over 10 years).[50,51] Pleomorphic lobular carcinoma in situ may increase that risk even further.[52] Radial scars are characterized microscopically by a fibroelastic core with radiating ducts and lobules. Radial scars and complex sclerosing lesions carry an 8–15% risk of DCIS or invasive malignancy at the time of excision.[47,53–57] Radial scars are usually managed by excisional biopsy.[45]

There are limited data with which to determine the optimal screening strategy after atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ. Breast MRI may improve breast cancer detection over mammography alone, but it is associated with more biopsies in this population.[58] The National Comprehensive Cancer Network is the only professional society with screening recommendations for those who have had atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ[45]:

- Annual mammography (not before age 30 years). Consider tomosynthesis.
- Consider annual breast MRI (not before age 25 years).
- Clinical breast examinations every 6–12 months.
- Engage in breast self-awareness (women should be familiar with their breasts and report changes to their health care provider promptly).

Past or Present Use of Hormonal Contraception

There have been conflicting data regarding the effect of hormonal contraception on breast cancer risk. A large meta-analysis in 1996 revealed a small increased risk of breast cancer among women with current or recent oral contraceptive use (RR 1.07, SD 0.02, $P<.001$).[59] Similar findings were noted in a large cohort study in 2017 (RR 1.20, 95% CI 1.14–1.26).[60] The absolute risk was quite small (one additional breast cancer diagnosis for every 7,690 women using hormonal contraception each year).[60] In both studies, breast cancer risk returned to baseline 5–10 years after discontinuing hormonal contraception.[59,60] Most studies do not suggest an increased risk of breast cancer among women using a levonorgestrel intrauterine system (IUS) or depo-medroxyprogesterone injections.[60–64] There are limited data regarding the etonogestrel implant, but no study to date has demonstrated an increased breast cancer risk.[63]

The risks of hormonal contraception must be weighed against the health, social, and economic consequences of unplanned pregnancy, as well as the many noncontraceptive benefits of hormonal contraception.[65] The maternal mortality rate in the United States in 2015 was 26.4 deaths per 100,000 pregnancies, which is comparable with the rate of excess breast cancer diagnoses (13 [95% CI 10–16]/100,000 person years) related to hormonal contraception suggested by the 2017 cohort study.[60,66]

Hormonal contraception, particularly oral contraceptives, significantly decreases the risk of ovarian and endometrial cancers.[67,68] There are no screening guidelines that specifically address exposure to hormonal contraception, so routine breast cancer screening is recommended in the absence of other risk factors for early-onset breast cancer.

Past or Present Use of Fertility Treatments

Many fertility treatments cause an increase in circulating estrogen and progesterone levels, which theoretically could increase future breast cancer risk.[69] Most studies have demonstrated no change or a decreased risk of breast cancer after fertility treatments.[59] Few studies specifically evaluated the risk of early-onset breast cancer. Very limited data suggest an increased risk of breast cancer among specific populations, including women exposed to many high-dose cycles of clomiphene citrate and women undergoing in vitro fertilization before age 24 years.[70,71] The American Society for Reproductive Medicine states that there is "fair evidence that fertility drugs are not associated with an increased risk of breast cancer (Grade B)."[69] No screening guidelines specifically address fertility treatment exposure, so routine breast cancer screening is recommended in the absence of other risk factors for early-onset breast cancer.

History of Radiation Exposure

Chest radiation therapy before age 30 years is a well-established risk factor for early-onset breast cancer.[45,72] Treatments of concern include mantle radiation for Hodgkin's lymphoma and moderate-dose chest radiation therapy for non-Hodgkin's lymphoma, leukemia, bone malignancies, or pediatric solid tumors (eg, Wilms tumor, neuroblastoma, and soft-tissue sarcoma). The cumulative incidence of invasive breast cancer in these patients is 13–20% by age 40–45 years, similar to that seen among *BRCA1* or *BRCA2* mutation carriers.[73–75] Risk is greatest among women treated with 40 Gy or more, but all women treated with 20 Gy or more are at increased risk for early-onset breast cancer.[73,74,76] This increased risk is evident 8–10 years after completion of radiation therapy and does not plateau at any point after treatment.[73–75,77]

Early initiation of breast cancer screening is effective for reducing stage at diagnosis in this population.[73] Both mammography and breast MRI are effective screening studies after chest radiation therapy, but mammography has higher specificity.[74,77–80] Multiple professional organizations have published screening guidelines for women with a history of chest radiation therapy (Table 4). There are limited data to suggest superiority of one screening protocol over others. Shared decision making,

Table 4. Screening Guidelines for Women With a History of Chest Radiation (20 Gy or More Total) Before Age 30

Intervention	National Comprehensive Cancer Network*	European Society of Breast Cancer Specialists†	International Late Effects of Childhood Cancer Guideline Harmonization Group‡
Age to initiate screening (use whichever is later)	Age 25 y or 10 y after radiation therapy	Age 30 y or 8 y after radiation therapy	Age 25 y or 8 y after radiation therapy
Breast MRI frequency	Annual, starting at age 25 y	Annual, starting at age 30 y	Annual MRI, mammography, or both (no definitive recommendation)
Mammography frequency	Annual, starting at age 30 y; consider tomosynthesis	Annual, starting at age 35 y	
Clinical breast examination	Every 6–12 mo	Not recommended	Not recommended
Breast self-awareness	Encouraged	Not addressed in guidelines	Not addressed in guidelines

MRI, magnetic resonance imaging.

* Data from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis. V.1.2019. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 12, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.

† Data from Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355–77.

‡ Data from Mulder RL, Kremer LC, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2013;14:e621–9.

including the discussion of risks of false positives and negatives, is recommended when deciding on a screening strategy.

Prior Breast or Ovarian Cancer

Breast cancer survivors remain at risk for a second breast cancer, but the risk for a second early-onset breast cancer among young breast cancer survivors is unknown. Among survivors of any age without a known cancer gene mutation, the risk of a second breast cancer is approximately 3% and 7% at 10 and 15 years after diagnosis, respectively.[81] There are no data regarding risk of early-onset breast cancer in women with ovarian cancer in childhood, adolescence, or early adulthood.

After breast cancer treatment, survivors require clinical and imaging follow-up to assess for recurrence and second malignancies. Both the National Comprehensive Cancer Network and the European Society of Breast Cancer Specialists recommend annual mammograms starting 6–12 months after completion of treatment.[52,82] Breast MRI should be considered in patients at high risk for a second cancer (eg, *BRCA1* or *BRCA2* mutation carriers)[52,82] (see Appendix 6 [http://links.lww.com/AOG/B869] for complete evidence summary).

EFFECT OF HEALTH DISPARITIES ON EARLY-ONSET BREAST CANCER

Objective measures of health disparities are well established, and health disparity populations[83] exhibit differences in rates of mammography screening, age at breast cancer diagnosis, stage at time of diagnosis, and rates of cancer treatment. African American women are significantly more likely to experience higher mortality from breast cancer compared with white women (Fig. 1).[84] Other health disparity groups, such as American Indians and Alaska Natives, Asians, Hispanics, and Native Hawaiians and other Pacific Islanders, are affected but often inadequately studied, as are sexual and gender minority persons.

The increased incidence of more-aggressive tumor types only partly explains the survival gap for black women.[6,85] Social determinants of health, such as systemic racism, poverty, and the environment, greatly affect cancer screening rates and outcomes.[86] Health literacy, childcare concerns, financial difficulties, and transportation affect the likelihood of receiving preventive health services such as mammography.[87,88]

Geography is a particularly important factor. Rural women are more likely to live in poor counties, with greater barriers to accessing primary care.[89] Poverty or lack of a regular primary care provider who recommends mammography is highly predictive of not being screened.[90,91] In general, poverty status correlates with more advanced stage at diagnosis, receiving less aggressive treatment, and higher risk of all-cause mortality.[92]

Physical proximity to urban centers is not a panacea. In 2014, African American women with breast cancer in Georgia living in isolated rural areas were 45% more likely to die than white women, whereas African American women living in urban areas were 24% more likely to die than white women.[92]

Provider-level bias and discrimination in breast cancer care treatment exist. For example, when genetic testing is indicated, African American women are less likely to be referred for genetic testing for pathogenic variants than white women.[93,94] African American women are also less likely to receive any type of lymph node surgery for axillary staging overall.[95]

Women of lower socioeconomic status are adversely affected by lack of health insurance coverage.[89] Cost affects primary care utilization and is a factor in patient decision making regarding mammography.[96] By one estimate, up to 37% of the mortality difference in breast cancer among black compared with white women can be attributed to disparities in health insurance.[97]

Intensive focus on modifiable system factors would be beneficial, such as expanding insurance coverage, addressing transportation barriers to appointments, and increasing access to primary care. The use of patient navigators and advocates, translator services, and tracking systems across different health systems could reduce the effect of limited health literacy, mistrust, and negative prior experiences with health care.[98] General practitioners who provide counseling and recommendations on health care preventive services can improve the rates of mammography for underscreened groups, such as recent immigrants.[99]

Bias by health care providers and health systems leading to disparate rates of services offered to patients should be corrected, and to further decrease differences in mortality, emphasis should be placed on ensuring equal treatment after diagnosis.[100] Groups such as the Black Women's Health Imperative are at the forefront of working to reduce these disparities, and can serve as a resource for both patients and health care providers. Efforts to promote quality improvement and adherence to national guidelines are important.

Breast cancer incidence is higher in younger African American women and other ethnic groups. In contrast, among postmenopausal women, breast

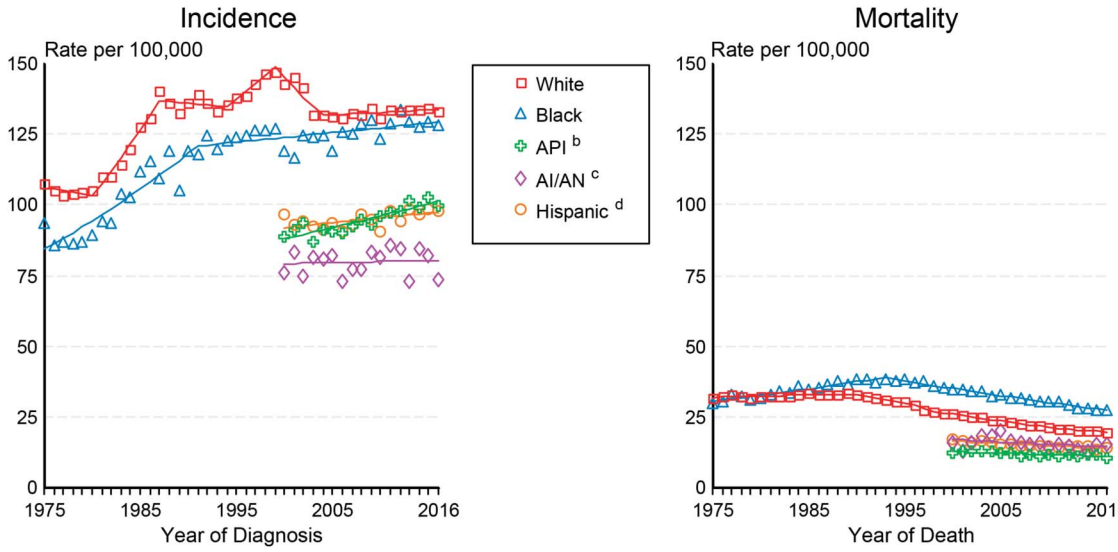

Fig. 1. Breast-cancer-specific mortality by race over time.*SEER incidence and U.S. death rates[a], cancer of the female breast. Joinpoint analyses for whites and blacks from 1975 to 2016 and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 2000 to 2016. Source: Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 21 areas (SEER 9 areas, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, Georgia excluding ATL/RG, Idaho, New York and Massachusetts). Mortality data are from U.S. Mortality Files, National Center for Health Statistics, CDC. [a]Rates are age-adjusted to the 2000 U.S. Std Population (19 age groups—Census P25-1103). Regression lines are calculated using the Joinpoint Regression Program Version 4.7, February 2019, National Cancer Institute. Joinpoint analyses for Whites and Blacks during the 1975–2015 period allow a maximum of 5 joinpoints. Analyses for other ethnic groups during the period 1992–2015 allow a maximum of 4 joinpoints. [b]API=Asian/Pacific Islander. [c]AI/AN=American Indian/Alaska Native. Rates for American Indian/Alaska Native are based on the Purchased/Referred Care Delivery Area (PRCDA) counties. [d]Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry. *Mortality decreased over time for white and black women, with overall higher mortality for black women. Reprinted from Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al, editors. SEER Cancer Statistics Review, 1975–2016. Bethesda, MD: National Cancer Institute; 2019. Available at: https://seer.cancer.gov/csr/1975_2016. Retrieved October 21, 2019.

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cancer incidence is highest in white women. The proportion of breast cancer diagnoses by age for nonwhite patients with breast cancer peaks in the late 40s, whereas diagnosis for white patients peaks in their 60s; this phenomenon is known as the crossover effect (Fig. 2).[101]

Most breast cancer research has been conducted on white women. Major professional society screening guidelines developed using this body of evidence might not be adequate for nonwhite populations. No national guidelines address this concern, but in 2018, the American College of Radiology commented that women at high risk, particularly black women and those of Ashkenazi Jewish descent, should be evaluated early in life to discuss potential benefit from supplemental screening.[102] Consideration should be given to encouraging screening before age 50 years, especially for African American women (see Appendix 7, available online at http://links.lww.com/AOG/B870, for complete evidence summary).

RISK-ASSESSMENT TOOLS

Although there are no validated tools or best practices specific to identifying risk factors or estimating the risk of early-onset breast cancer, there are multiple tools that may be helpful to identify short-term risk in younger women. Current best practices aim to identify women at risk of familial cancer syndromes on the basis of family history to determine who may benefit from genetic testing.

The three most widely used tools for predicting *BRCA* gene carrier probability are BRCAPRO, BOADICEA (the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), and Penn II.[103] BRCAPRO and BOADICEA also provide cancer risk estimates in addition to estimates of

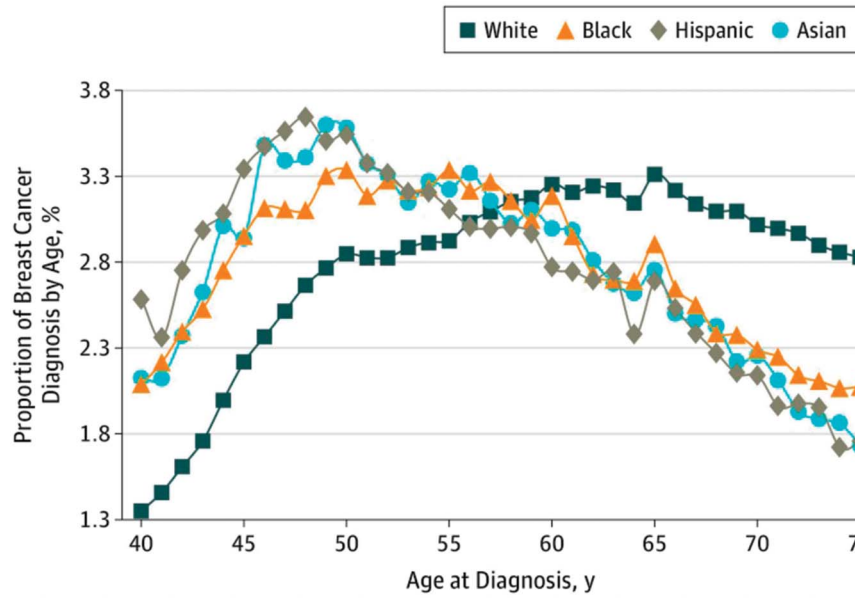

Fig. 2. The cross-over effect: age at diagnosis for women with breast cancer, by race.* *The proportion of breast cancer diagnoses by age for nonwhite patients with breast cancer peaks in the late 40s, while diagnosis of white patients peaks in their 60s. Reproduced with permission from JAMA Surg 2018;153(6):594–595. ©2018 American Medical Association. All rights reserved.

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likelihood of genetic mutations. These models might be useful to direct women to genetic testing and counseling who are at increased risk of genetic mutations that pose a high risk of early-onset disease. BRCAPRO is a validated statistical program to estimate individual carrier probabilities on the basis of family history. It is not specific to any age range and does not directly estimate the risk of early-onset cancer, but rather the risk of carrying a *BRCA1* or *BRCA2* mutation. BOADICEA likewise was developed using population data from families in the United Kingdom to create a model based on family history and requires detailed family pedigree. The Penn II model uses clinical questions based on family history to reach a carrier probability, but does not calculate cancer risks. Once a *BRCA1* or *BRCA2* mutation is identified the Stanford risk-assessment tool for *BRCA* carriers may aid in decision making for preventive measures based as it provides age-related risk of cancer and compares multiple intervention strategies.[104]

Additional widely validated models to assess cancer risk include the Tyrer-Cuzick, modified Gail, and Breast Cancer Surveillance Consortium models. None specifically assess risk of early-onset or premenopausal breast cancer, although most provide estimated 5- or 10-year cancer risk as well as lifetime risk of breast cancer. No models used validation cohorts with patients younger than 20 years. The modified Gail model has been validated in women 35 years and older to assess 5-year invasive cancer risk.[105] The Tyrer-Cuzick model has been studied in women older than age 20 years to assess 10-year cancer risk and has been shown to perform better in women with a family history of breast cancer.[106] The Breast Cancer Surveillance Consortium risk calculator is validated for women older than age 35 years to provide 5- and 10-year risks and includes family history factors as well as breast density in the calculation.[107] There are limited data on the use of these models to specifically address cancer risk reduction in young women.

Family history should be collected and updated periodically to identify patients who may be at increased risk of predisposing genetic mutations. Tools that may aid in collecting family history are the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7.[12,13] There is no evidence to recommend one method over another. Those who screen positive or who meet published guidelines for qualifying family histories should be referred for genetic counseling and testing.[13]

There are no guidelines or best practices for identifying risk factors or for the use of tools to estimate risk specific to early-onset breast cancer. However, multiple organizations provide guidance for assessing risk of breast cancer in general.

The U.S. Preventive Services Task Force advocates use of brief familial assessment tools to assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1* or *BRCA2* gene mutations. The U.S. Preventive Services Task Force reviewed six tools that were adequately validated, but

found insufficient evidence to recommend one tool over another.[12] Other organizations likewise do not advocate for use of any specific tool.[14,108–111]

National Comprehensive Cancer Network guidelines on breast cancer risk reduction recommend assessing family history and referring to genetic counseling when appropriate as well as use of the modified Gail or Tyrer-Cuzick model to assess risk among women older than age 34 years.[112] The National Comprehensive Cancer Network has also established criteria for genetic testing for high-risk mutations.[13] These guidelines recommend assessment no earlier than age 18 years based on family history. No specific tool is recommended, and the recommendations are not specific to reducing the risk of early-onset cancer (see Appendix 8, available online at http://links.lww.com/AOG/B871, for complete evidence summary).

COMMUNICATING RISK

Shared decision making is a key component of patient-centered health care, particularly because there is often more than one option for screening. Although patient decision aids and risk calculators help enumerate risk and are adjuncts to shared decision making, the process is more involved.[113] Using narrative risk communication strategies,[114] communicating absolute rather than RR,[115] and managing framing bias[116] are important considerations in communicating risk of early-onset breast cancer.

Many decision aids and calculators are directed to specific populations (eg, subtypes or age ranges), but none are specific for communicating risk of early-onset breast cancer. Several tools may be useful:

- Families Sharing Health Assessment and Risk Evaluation (Families SHARE, a product of the National Institutes of Health's National Human Genome Research Institute) is a decision aid that is useful for shared decision making for individuals of varied age groups and can be used within and outside of an office setting.[117]
- Breast Screening Decisions (developed collaboratively by the Weill Cornell Medical College and Sloan Kettering Cancer Center) is directed to women aged 40–49 years.[118]
- Breast Cancer Screening (PDQ) has both a patient and health care provider tool, which can be used as companion documents.[119]
- The University of Wisconsin School of Public Health's Health Decision tool was originally created and tested at the University of California, San Francisco.[120–122] It includes a breast cancer screening module that can be integrated into some electronic health record systems.

Studies of decision aids for breast cancer prevention in *BRCA1* and *BRCA2* mutation carriers demonstrated that cancer-related distress was reduced among those who used a decision aid compared with those who did not. Decisional conflict did not change with use of the aid.[123,124] The following tools may be useful for women at high risk of hereditary breast and ovarian cancer:

- The Cancer Risk Education Intervention Tool is a web-based (noninteractive) adjunctive tool for use in low socioeconomic settings and among ethnically diverse women.[125]
- The Stanford Shared Decision Making Tool for women with *BRCA1* or *BRCA2* was developed to guide decision making about screening and treatment based on calculated risk.[104]

For minority groups, the Health Belief Model was used as a construct for developing a school-based classroom and online tool that increased knowledge about breast cancer risk among African American women aged 20–39 years.[126]

Because we anticipated that a literature search would find limited information specific to communicating risk of early-onset breast cancer, we deliberately conducted a broad search encompassing other aspects of breast cancer and other cancers and health conditions. Patient decision aids for colorectal cancer screening have been shown to improve knowledge and interest in screening compared with no information, but are no better than general colorectal cancer screening information.[127] Healthwise Knowledge Base is an evidence-based interactive platform to inform patients about mammogram initiation that includes a shared decision making breast cancer screening tool for women aged 40–50 years (see Appendix 9, available online at http://links.lww.com/AOG/B872), as well as a tool for assisting in decisions about *BRCA* testing. The user's concerns, desires, and fears are weighed in response to evidence provided about the risks and benefits of screening, and a score indicating preferences and readiness for screening is calculated.[128] A decision analytic model was used to improve estimation of benefits and risks for patients undergoing thrombolysis, with the added benefit that this computerized decision aid can be embedded in an electronic health record.[129] This approach could be translated to support integration of the Gail or Families SHARE model, for example, into a primary care or a woman's personal electronic health record.

There are no current major professional society or health services guidelines about communicating the

risk for early-onset breast cancer. Shared decision making has been endorsed by ACOG for deciding the age at which to initiate breast cancer screening.[109] The American College of Obstetricians and Gynecologists acknowledges the importance of screening for social determinants of health in all patients, as these factors may influence decision making and communication.[86]

U.S. Preventive Services Task Force guidelines do not address early-onset breast cancer risk, except to state that the recommended screening guidelines do not apply to women with prior chest radiation or known underlying genetic mutations such as *BRCA1* or *BRCA2*. National Institute of Health Care Excellence guidelines recommend providing information and support for decision making, but do not recommend any specific tool or decision aid. National Institute of Health Care Excellence guidelines regarding familial breast cancer also recommend the use of shared decision making, materials, and decision aids as well as standardizing the discussion involved in counseling patients and families at risk for familial breast cancers[108] (see Appendix 9 [http://links.lww.com/AOG/B872] for complete evidence summary).

RISK-REDUCTION STRATEGIES

There is limited evidence for risk modification specific to the outcome of early-onset breast cancer. The evidence for risk reduction among younger women is most robust for *BRCA* mutation carriers.

Risk-reducing bilateral mastectomy should be considered in women with a genetic mutation conferring a high risk of breast cancer.[112] There are no guidelines or studies addressing the age at which risk-reducing mastectomies should be undertaken. Age-related risk estimation tables may be useful to counsel women with *BRCA* mutations on the timing of prophylactic procedures.[130] There is no evidence supporting risk-reducing mastectomies for women with low-risk genes or whose risk is based on nonhereditary factors alone.

We found no evidence to support oophorectomy for the purposes of preventing early-onset breast cancer. The use of bilateral salpingo-oophorectomy to prevent lifetime risk of breast and ovarian cancer has been estimated to be as high as 50% for *BRCA1* and *BRCA2* carriers, although more recent publications question these results.[131]

There are no guidelines or studies about the use of risk-reducing agents expressly for the purpose of reducing the risk of early-onset breast cancer. Tamoxifen is the only agent indicated for use in premenopausal women at increased risk of breast cancer, and is recommended for women with 5-year risk of 1.7% or higher. The risks and benefits in women younger than 35 years is not known.[112] Most large trials of chemoprevention were performed in older women who had completed menopause. The National Surgical Adjuvant Breast and Bowel Project P-1 trial found a 44% decrease in cancer among women younger than 50 years treated with tamoxifen for chemoprevention.[132]

There are limited data regarding the magnitude of risk reduction with the use of tamoxifen for *BRCA1* and *BRCA2* mutation carriers or women with prior thoracic radiation. However, cohort data suggest there might be a benefit for *BRCA2* carriers; the National Surgical Adjuvant Breast and Bowel Project P-1 study showed a nonsignificant 62% decrease relative to placebo (RR 0.38, 95% CI 0.06–1.56).[112,132] Although other European studies have shown mixed effects, this overall reduction is supported by a systemic review of randomized controlled prevention trials across all studied populations showing a 44% decrease in the risk of breast cancer for women younger than 50 (hazard ratio 0.66, 95% CI 0.52–0.85).[133]

There is limited evidence for the modification of health behaviors to reduce the risk of early-onset breast cancer. A recent meta-analysis assessed numerous risk factors for *BRCA* carriers.[134] Later age at the time of first live birth was associated with a decreased lifetime risk of breast cancer for *BRCA1* carriers (effect size for women aged 30 years or older=0.65 vs women aged younger than 30 years, 95% CI 0.42–0.99). There was no effect of age at first birth for *BRCA2* carriers.

Breastfeeding also appeared protective for lifetime risk of cancer for *BRCA1* carriers, although meta-analysis could not be performed because of study heterogeneity. Reported effects based on case–control studies showed a 32–50% decreased risk if breastfeeding continued for more than 1 year compared with never breastfeeding. Additionally, three or more live births also appeared to have a protective effect for *BRCA1* carriers (effect size=0.57, 95% CI 0.39–0.85) as well as *BRCA2* carriers (effect size=0.52, 95% CI 0.30–0.86), compared with nulliparity. For *BRCA1* or *BRCA2* carriers, there were no significant or reliably duplicated results of effects of alcohol consumption, oral contraceptive use, or smoking.[134,135] In review articles on risk factors for women at average risk, there was no reliable effect seen for alcohol consumption or modification of other dietary factors for premenopausal breast cancer.[136,137]

There are no guidelines specific to the prevention of early-onset breast cancer. Those that may be considered relevant address lifetime breast cancer risk reduction, largely among women older than age 35 years. The National Comprehensive Cancer Network

recommends tamoxifen, 20 mg/d, for up to 5 years for women aged 35 years and older with a high 5-year risk of breast cancer, defined as a 5-year risk of 1.7% or higher using the Gail model, or prior lobular carcinoma in situ.[112] U.S. Preventive Services Task Force guidelines for reducing the risk of primary cancer state that women at increased risk should engage in shared decision making regarding chemoprevention.

The National Comprehensive Cancer Network advises a healthy lifestyle for reduction of risk for breast cancer for all women, though the magnitude of this reduction and whether it reduces the risk of early-onset breast cancer or premenopausal breast cancer is unknown.[97] Elements of healthy lifestyle advised by the National Comprehensive Cancer Network include limited alcohol consumption, vigorous physical activity, maintaining a healthy weight, and breastfeeding (see Appendix 10, available online at http://links.lww.com/AOG/B873, for complete evidence summary).

Breast self-examination is no longer part of major society guidelines for average risk women given the high number of false positives and absence of supportive evidence for benefit.[2,12,109] Our literature review found no evidence for its use in women at risk for early-onset breast cancer, but women should be counseled to be familiar with their breasts and promptly report changes to their breasts to their health care provider.

SPECIAL CONSIDERATIONS FOR EARLY-ONSET BREAST CANCER

Survivorship in women with early-onset breast cancer is a critical component to initial evaluation and treatment as well as ongoing care. Chemotherapy is often and variably responsible for chemotherapy-induced amenorrhea, menopause, or true ovarian failure, resulting in consequences such as infertility or subfertility, bone loss, and increased cardiac risk as well as menopausal symptoms, which can have a significant effect on quality of life. Age at diagnosis, receptor status, and treatment regimen are important considerations in managing ongoing care for women affected by early-onset breast cancer.

The National Comprehensive Cancer Network and the American Society of Clinical Oncology have produced comprehensive guidelines for survivorship.[138,139] The American Cancer Society and the American Society of Clinical Oncology jointly created survivorship guidelines after systematic review in 2015.[140] Although not specific for early-onset breast cancer, ACOG provides resources about managing gynecologic issues in women with breast cancer, many of which are applicable for women with early-onset breast cancer.[141] The American College of Obstetricians and Gynecologists recommendations include use of nonhormonal interventions for symptomatic patients, because data are conflicting about the deleterious effects of hormone therapy on recurrence and overall survival rates.[141] Although not specific to women with early-onset breast cancer, the North American Menopause Society and the International Society on Women's Sexual Health have coauthored recommendations regarding the treatment of genitourinary syndrome of menopause in women with breast cancer.[142]

Management of women who have or have had early-onset breast cancer should include attention to the issues of contraception, fertility, and pregnancy:

- Effective contraception is often overlooked as part of the treatment regimen for patients with early-onset breast cancer, and family planning consultation should be considered.[143] The copper IUS is the preferred contraceptive method for women with breast cancer, although the levonorgestrel IUS can safely be used in combination with tamoxifen.[144,145] The preferred method of emergency contraception is the copper-containing IUS, although progestin regimens can also be used.[146]
- All women with early-onset breast cancer should have fertility preservation counseling.[147] Oocyte and embryo cryopreservation is considered first-line treatment.[147] Treatment with gonadotropin-releasing hormone agonist during chemotherapy should be considered when ovarian oocyte and embryo cryopreservation is not possible; it affords some protection to the ovary and is associated with increased fertility rates when compared with no treatment.[148] Aromatase inhibitors and gonadotropin-releasing hormone agonist triggers should be used when employing controlled ovarian stimulation for women undergoing fertility treatments with a history of early-onset breast cancer to lower estrogen levels.[149] Prenatal genetic diagnosis should be considered in women with *BRCA* mutations or other documented germ line mutations undergoing in vitro fertilization procedures. Ovarian tissue harvesting offers a promising alternative to cryopreservation therapies.[149]
- Pregnancy after a diagnosis of early-onset breast cancer has not been shown to increase the risk of recurrence.[150] When considering timing, pregnancy occurring at least 10 months after breast cancer diagnosis was not found to be harmful and may even contribute to survivorship.[151] When breast cancer is diagnosed in pregnancy, chemotherapy can be safely instituted in the second and third trimesters.[150]

See Appendix 1 (http://links.lww.com/AOG/B864) for complete evidence summary.

RESEARCH GAPS AND OPPORTUNITIES

The evidence review and subsequent stakeholder discussion revealed the following research gaps and opportunities for early-onset breast cancer (see Appendix 11, available online at http://links.lww.com/AOG/B874, for a more in-depth assessment):

- Develop risk-assessment tools specific to early-onset breast cancer
- Optimize integration of risk assessment into primary care visits and electronic health records
- Obtain data on and determine optimal screening for nonwhite populations
- Determine risks associated with dense breasts in young women
- Determine appropriate adjunctive screening for young women with dense breasts
- Validate epidemiologic data largely based on European populations in U.S. women, including underrepresented subgroups
- Develop strategies to eliminate implicit bias among health care providers and medical systems
- Expand screening, genetic counseling, and testing among high-risk women
- Develop and validate tools for communicating early-onset breast cancer risk to patients
- Develop and validate training techniques for health care providers to screen, test, and initiate risk-reducing strategies in women at risk for early-onset breast cancer
- Determine safety and optimal timing of pregnancy after treatment for early-onset breast cancer
- Optimize fertility preservation in women undergoing treatment for early-onset breast cancer

REFERENCES

1. National Cancer Institute. Cancer stat fact: female breast cancer. Available at: https://seer.cancer.gov/statfacts/html/breast.html. Retrieved October 22, 2019.
2. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society [published erratum appears in JAMA 2016;315:1406]. JAMA 2015;314:1599–614.
3. Centers for Disease Control and Prevention. Breast cancer: black women have higher death rates from breast cancer than other women.Available at: https://www.cdc.gov/vitalsigns/BreastCancer/?s_cid=bb-vitalsigns-103. Retrieved October 21, 2019.
4. U.S. Cancer Statistics Working Group. U.S. cancer statistics data visualizations tool, based on November 2018 submission data (1999-2016). Available at: https://gis.cdc.gov/Cancer/USCS/DataViz.html. Retrieved October 23, 2019.
5. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg 2009;208:341–7.
6. Ademuyiwa FO, Gao F, Hao L, Morgensztern D, Aft RL, Ma CX, et al. US breast cancer mortality trends in young women according to race. Cancer 2015;121:1469–76.
7. Hartge P, Struewing JP, Wacholder S, Brody LC, Tucker MA. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. Am J Hum Genet 1999;64:963–70.
8. Metcalfe KA, Poll A, Royer R, Llacuachaqui M, Tulman A, Sun P, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol 2010;28:387–91.
9. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al, editors. SEER cancer statistics review, 1975–2016. Available at: https://seer.cancer.gov/csr/1975_2016. Retrieved October 21, 2019.
10. Newman LA. Breast cancer in African-American women. Oncologist 2005;10:1–14.
11. Stead LA, Lash TL, Sobieraj JE, Chi DD, Westrup JL, Charlot M, et al. Triple-negative breast cancers are increased in black women regardless of age or body mass index. Breast Cancer Res 2009;11:R18.
12. U.S. Preventive Services Task Force. BRCA-related cancer: risk assessment, genetic counseling, and genetic testing. Final recommendation statement. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing. Retrieved October 23, 2019.
13. National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast and ovarian. Version 3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Retrieved October 22, 2019.
14. Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110–26.
15. Vos JR, de Bock GH, Teixeira N, van der Kolk DM, Jansen L, Mourits MJ, et al. Proven non-carriers in BRCA families have an earlier age of onset of breast cancer. Eur J Cancer 2013;49:2101–6.
16. Moller P, Stormorken A, Holmen MM, Hagen AI, Vabo A, Maehle L. The clinical utility of genetic testing in breast cancer kindreds: a prospective study in families without a demonstrable BRCA mutation. Breast Cancer Res Treat 2014;144:607–14.
17. Brandt A, Lorenzo Bermejo J, Sundquist J, Hemminki K. Breast cancer risk in women who fulfill high-risk criteria: at what age should surveillance start? Breast Cancer Res Treat 2010;121:133–41.
18. Colditz GA, Kaphingst KA, Hankinson SE, Rosner B. Family history and risk of breast cancer: nurses' health study. Breast Cancer Res Treat 2012;133:1097–104.
19. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997;71:800–9.
20. Parmigiani G, Chen S, Iversen ES Jr, Friebel TM, Finkelstein DM, Anton-Culver H, et al. Validity of models for predicting BRCA1 and BRCA2 mutations. Ann Intern Med 2007;147:441–50.
21. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast

screening with MRI as an adjunct to mammography. American Cancer Society Breast Cancer Advisory Group [published erratum appears in CA Cancer J Clin 2007;57:185]. CA Cancer J Clin 2007;57:75–89.

22. National Human Genome Research Institute. Genomic education websites. Available at: https://www.genome.gov/about-genomics/teaching-tools/Genomics-Education-Websites. Retrieved October 22, 2019.
23. Lancaster JM, Powell CB, Chen LM, Richardson DL. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. SGO Clinical Practice Committee. Gynecol Oncol 2015;136:3–7.
24. American Society of Clinical Oncology. Genetics toolkit. Available at: https://www.asco.org/practice-policy/cancer-care-initiatives/genetics-toolkit. Retrieved April 20, 2020.
25. Oros KK, Ghadirian P, Maugard CM, Perret C, Paredes Y, Mes-Masson AM, et al. Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent. Clin Genet 2006; 70:320–9.
26. Evans DG, Eccles DM, Rahman N, Young K, Bulman M, Amir E, et al. A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO. J Med Genet 2004;41:474–80.
27. Bellcross CA, Lemke AA, Pape LS, Tess AL, Meisner LT. Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. Genet Med 2009;11:783–9.
28. Hoskins KF, Zwaagstra A, Ranz M. Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. Cancer 2006;107:1769–76.
29. Ashton-Prolla P, Giacomazzi J, Schmidt AV, Roth FL, Palmero EI, Kalakun L, et al. Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. BMC Cancer 2009;9:28–283.
30. Robson ME, Bradbury AR, Arun B, Domchek SM, Ford JM, Hampel HL, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol 2015;33:3660–7.
31. Beck AC, Yuan H, Liao J, Imperiale P, Shipley K, Erdahl LM, et al. Rate of BRCA mutation in patients tested under NCCN genetic testing criteria. Am J Surg 2020;219:145–49.
32. Neben CL, Zimmer AD, Stedden W, van den Akker J, O'Connor R, Chan RC, et al. Multi-gene panel testing of 23,179 individuals for hereditary cancer risk identifies pathogenic variant carriers missed by current genetic testing guidelines. J Mol Diagn 2019;21:646–57.
33. Counseling about genetic testing and communication of genetic test results. Committee Opinion No. 693. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:771–2.
34. Christianson CA, Powell KP, Hahn SE, Blanton SH, Bogacik J, Henrich VC. The use of a family history risk assessment tool within a community health care system: views of primary care providers. Genomedical Connection. J Genet Couns 2012;21: 652–61.
35. Beitsch PD, Whitworth PW, Hughes K, Patel R, Rosen B, Compagnoni G, et al. Underdiagnosis of hereditary breast cancer: are genetic testing guidelines a tool or an obstacle? J Clin Oncol 2019;37:453–60.
36. Yang S, Axilbund JE, O'Leary E, Michalski ST, Evans R, Lincoln SE, et al. Underdiagnosis of hereditary breast and ovarian cancer in Medicare patients: genetic testing criteria miss the mark. Ann Surg Oncol 2018;25:2925–31.
37. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med 2012;156:635–48.
38. Kim BK, Choi YH, Nguyen TL, Nam SJ, Lee JE, Hopper JL, et al. Mammographic density and risk of breast cancer in Korean women. Eur J Cancer Prev 2015;24:422–9.
39. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–69.
40. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography [published erratum appears in Ann Intern Med 2003;138:771]. Ann Intern Med 2003;138:168–75.
41. McCarthy AM, Barlow WE, Conant EF, Haas JS, Li CI, Sprague BL, et al. Breast cancer with a poor prognosis diagnosed after screening mammography with negative results. PROSPR Consortium [published erratum appears in JAMA Oncol 2018;4:1018]. JAMA Oncol 2018;4:998–1001.
42. van der Waal D, Verbeek ALM, Broeders MJ. Breast density and breast cancer-specific survival by detection mode. BMC Cancer 2018;18:38–7.
43. Bertrand KA, Tamimi RM, Scott CG, Jensen MR, Pankratz V, Visscher D, et al. Mammographic density and risk of breast cancer by age and tumor characteristics. Breast Cancer Res 2013;15:R104.
44. Berg WA, Harvey JA. Breast density and supplemental screening. Available at: https://www.sbi-online.org/RESOURCES/WhitePapers/TabId/595/ArtMID/1617/ArticleID/596/Breast-Density-and-Supplemental-Screening.aspx. Retrieved October 21, 2019.
45. National Comprehensive Cancer Network. Breast cancer screening and diagnosis. Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Retrieved October 22, 2019.
46. Management of women with dense breasts diagnosed by mammography. Committee Opinion No. 625. American College of Obstetricians and Gynecologists [published erratum appears in Obstet Gynecol 2016;127:166]. Obstet Gynecol 2015;125:750–1.
47. American Society of Breast Surgeons. Consensus guideline on genetic testing for hereditary breast cancer. Available at: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Retrieved October 21, 2019.
48. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast–risk assessment and management options. N Engl J Med 2015;372:78–89.
49. Dyrstad SW, Yan Y, Fowler AM, Colditz GA. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis. Breast Cancer Res Treat 2015;149:569–75.
50. Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. Nat Rev Clin Oncol 2015;12:227–38.
51. Chuba PJ, Hamre MR, Yap J, Severson RK, Lucas D, Shamsa F, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. J Clin Oncol 2005;23:5534–41.
52. National Comprehensive Cancer Network. Breast cancer. Version 3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Retrieved October 29, 2019.

53. Linda A, Zuiani C, Furlan A, Londero V, Girometti R, Machin P, et al. Radial scars without atypia diagnosed at imaging-guided needle biopsy: how often is associated malignancy found at subsequent surgical excision, and do mammography and sonography predict which lesions are malignant?. AJR Am J Roentgenol 2010;194:1146–51.

54. Patterson JA, Scott M, Anderson N, Kirk SJ. Radial scar, complex sclerosing lesion and risk of breast cancer. Analysis of 175 cases in Northern Ireland. Eur J Surg Oncol 2004;30:1065–8.

55. Diagnosis and management of benign breast disorders. Practice Bulletin No. 164. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;127:e141–56.

56. Bunting DM, Steel JR, Holgate CS, Watkins RM. Long term follow-up and risk of breast cancer after a radial scar or complex sclerosing lesion has been identified in a benign open breast biopsy. Eur J Surg Oncol 2011;37:709–13.

57. Rungruang B, Kelley JL III. Benign breast diseases: epidemiology, evaluation, and management. Clin Obstet Gynecol 2011;54:110–24.

58. Port ER, Park A, Borgen PI, Morris E, Montgomery LL. Results of MRI screening for breast cancer in high-risk patients with LCIS and atypical hyperplasia. Ann Surg Oncol 2007;14:1051–7.

59. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347:1713–27.

60. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 2017;377:2228–39.

61. Dinger J, Bardenheuer K, Minh TD. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. Contraception 2011;83:211–7.

62. Jareid M, Thalabard JC, Aarflot M, Bovelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. Gynecol Oncol 2018;149:127–32.

63. Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, et al. Progestin and breast cancer risk: a systematic review. Breast Cancer Res Treat 2016;155:3–12.

64. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. Cancer Res 2012;72:2028–35.

65. Sonfield A, Kost K. Public costs from unintended pregnancies and the role of public insurance programs in paying for pregnancy-related care: national and state estimates for 2010. Available at: https://www.guttmacher.org/report/public-costs-unintended-pregnancies-and-role-public-insurance-programs-paying-pregnancy. Retrieved October 22, 2019.

66. Global, regional, and national levels of maternal mortality, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. GBD 2015 Maternal Mortality Collaborators [published erratum appears in Lancet 2017;389:e1]. Lancet 2016;388:1775–812.

67. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, et al. Hormonal contraception and risk of cancer. Hum Reprod Update 2010;16:631–50.

68. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. JAMA Oncol 2018;4:516–21.

69. Fertility drugs and cancer: a guideline. Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2016;106:1617–26.

70. Brinton LA, Scoccia B, Moghissi KS, Westhoff CL, Niwa S, Ruggieri D, et al. Long-term relationship of ovulation-stimulating drugs to breast cancer risk. Cancer Epidemiol Biomarkers Prev 2014;23:584–93.

71. Stewart LM, Holman CD, Hart R, Bulsara MK, Preen DB, Finn JC. In vitro fertilization and breast cancer: is there cause for concern? Fertil Steril 2012;98:334–40.

72. Gynecologic issues in children and adolescent cancer patients and survivors. ACOG Committee Opinion No. 747. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e67–77.

73. Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med 2010;152:44–54.

74. Mulder RL, Kremer LC, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2013;14:e621–9.

75. National Cancer Institute. Breast cancer screening (PDQ®)–health professional version. Available at: https://www.cancer.gov/types/breast/hp/breast-screening-pdq. Retrieved October 22, 2019.

76. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27:3901–7.

77. National Cancer Institute. Breast cancer prevention (PDQ®)–health professional version. Available at: https://www.cancer.gov/types/breast/hp/breast-prevention-pdq. Retrieved October 22, 2019.

78. Allen SD, Wallis MG, Cooke R, Swerdlow AJ. Radiologic features of breast cancer after mantle radiation therapy for Hodgkin disease: a study of 230 cases. Radiology 2014;272:73–8.

79. Koo E, Henderson MA, Dwyer M, Skandarajah AR. Management and prevention of breast cancer after radiation to the chest for childhood, adolescent, and young adulthood malignancy. Ann Surg Oncol 2015;22(suppl 3):S545–51.

80. Terenziani M, Casalini P, Scaperrotta G, Gandola L, Trecate G, Catania S, et al. Occurrence of breast cancer after chest wall irradiation for pediatric cancer, as detected by a multimodal screening program. Int J Radiat Oncol Biol Phys 2013;85:35–9.

81. Pierce LJ, Levin AM, Rebbeck TR, Ben-David MA, Friedman E, Solin LJ, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006;24:2437–43.

82. Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355–77.

83. National Institutes of Health. NIH health disparities strategic plan and budget: fiscal years 2009–2013. Available at: https://www.nimhd.nih.gov/docs/2009-2013nih_health_disparities_strategic_plan_and_budget.pdf. Retrieved April 20, 2020.

84. Wheeler SB, Reeder-Hayes KE, Carey LA. Disparities in breast cancer treatment and outcomes: biological, social, and

health system determinants and opportunities for research. Oncologist 2013;18:986–93.

85. Newman LA, Bunner S, Carolin K, Bouwman D, Kosir MA, White M, et al. Ethnicity related differences in the survival of young breast carcinoma patients. Cancer 2002;95:21–7.
86. Importance of social determinants of health and cultural awareness in the delivery of reproductive health care. ACOG Committee Opinion No. 729. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e43–8.
87. Jacobs EA, Rathouz PJ, Karavolos K, Everson-Rose SA, Janssen I, Kravitz HM, et al. Perceived discrimination is associated with reduced breast and cervical cancer screening: the Study of Women's Health Across the Nation (SWAN). J Womens Health (Larchmt) 2014;23:138–45.
88. Mishra SI, DeForge B, Barnet B, Ntiri S, Grant L. Social determinants of breast cancer screening in urban primary care practices: a community-engaged formative study. Womens Health Issues 2012;22:e429–38.
89. Health disparities in rural women. Committee Opinion No. 586. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:384–8.
90. Schueler KM, Chu PW, Smith-Bindman R. Factors associated with mammography utilization: a systematic quantitative review of the literature. J Womens Health (Larchmt) 2008; 17:1477–98.
91. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69:438–51.
92. Markossian TW, Hines RB, Bayakly R. Geographic and racial disparities in breast cancer-related outcomes in Georgia. Health Serv Res 2014;49:481–501.
93. Jones TP, Katapodi MC, Lockhart JS. Factors influencing breast cancer screening and risk assessment among young African American women: an integrative review of the literature. J Am Assoc Nurse Pract 2015;27:521–9.
94. Cragun D, Bonner D, Kim J, Akbari MR, Narod SA, Gomez-Fuego A, et al. Factors associated with genetic counseling and BRCA testing in a population-based sample of young Black women with breast cancer. Breast Cancer Res Treat 2015;151: 169–76.
95. Reeder-Hayes KE, Bainbridge J, Meyer AM, Amos KD, Weiner BJ, Godley PA, et al. Race and age disparities in receipt of sentinel lymph node biopsy for early-stage breast cancer. Breast Cancer Res Treat 2011;128:863–71.
96. Racial and ethnic disparities in obstetrics and gynecology. Committee Opinion No. 649. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:e130–4.
97. Jemal A, Robbins AS, Lin CC, Flanders WD, DeSantis CE, Ward EM, et al. Factors that contributed to black-white disparities in survival among nonelderly women with breast cancer between 2004 and 2013. J Clin Oncol 2018;36:14–24.
98. Reeder-Hayes KE, Anderson BO. Breast cancer disparities at home and abroad: a review of the challenges and opportunities for system-level change. Clin Cancer Res 2017;23:2655–64.
99. Lee-Lin F, Nguyen T, Pedhiwala N, Dieckmann N, Menon U. Mammography screening of Chinese immigrant women: ever screened versus never screened. Oncol Nurs Forum 2015;42: 470–8.
100. Rosenzweig M, Brufsky A, Rastogi P, Puhalla S, Simon J, Underwood S. The attitudes, communication, treatment, and support intervention to reduce breast cancer treatment disparity. Oncol Nurs Forum 2011;38:85–9.
101. Stapleton SM, Oseni TO, Bababekov YJ, Hung YC, Chang DC. Race/ethnicity and age distribution of breast cancer diagnosis in the United States. JAMA Surg 2018;153:594–5.
102. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA. Breast cancer screening in women at higher-than-average risk: recommendations from the ACR. J Am Coll Radiol 2018;15:408–14.
103. Antoniou AC, Hardy R, Walker L, Evans DG, Shenton A, Eeles R, et al. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet 2008;45:425–31.
104. Kurian AW, Munoz DF, Rust P, Schackmann EA, Smith M, Clarke L, et al. Online tool to guide decisions for BRCA1/2 mutation carriers. J Clin Oncol 2012;30:497–506.
105. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst 2001;93:358–66.
106. Terry MB, Liao Y, Whittemore AS, Leoce N, Buchsbaum R, Zeinomar N, et al. 10-year performance of four models of breast cancer risk: a validation study. Lancet Oncol 2019;20: 504–17.
107. Vachon CM, Pankratz VS, Scott CG, Haeberle L, Ziv E, Jensen MR, et al. The contributions of breast density and common genetic variation to breast cancer risk. J Natl Cancer Inst 2015;107:pii: dju397.
108. National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical Guideline CG164. Available at: https://www.nice.org.uk/guidance/cg164/evidence. Retrieved October 22, 2019.
109. Breast cancer risk assessment and screening in average-risk women. Practice Bulletin No. 179. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e1–16.
110. Family history as a risk assessment tool. Committee Opinion No. 478. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:747–50.
111. Hereditary cancer syndromes and risk assessment. ACOG Committee Opinion No. 793. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e143–9.
112. National Comprehensive Cancer Network. Breast cancer risk reduction. Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf. Retrieved October 22, 2019.
113. National Learning Consortium. Shared decision making. Fact sheet. Available at: https://www.healthit.gov/sites/default/files/nlc_shared_decision_making_fact_sheet.pdf. Retrieved October 21, 2019.
114. Kreuter MW, Green MC, Cappella JN, Slater MD, Wise ME, Storey D, et al. Narrative communication in cancer prevention and control: a framework to guide research and application. Ann Behav Med 2007;33:221–35.
115. Zipkin DA, Umscheid CA, Keating NL, Allen E, Aung K, Beyth R, et al. Evidence-based risk communication: a systematic review. Ann Intern Med 2014;161:270–80.
116. Garcia-Retamero R, Cokely ET. Communicating health risks with visual aids. Curr Dir Psychol Sci 2013;22:392–9.
117. National Human Genome Research Institute. Families SHARE – Sharing health Assessment and Risk evaluation. Available at: https://www.genome.gov/research-at-nhgri/Projects/Families-SHARE. Retrieved October 22, 2019.

118. Weill Cornell Medical College. Breast screening decisions. Available at: https://bsd.weill.cornell.edu/#/. Retrieved October 23, 2019.

119. National Cancer Institute. Genetics of breast and gynecologic cancers (PDQ®)–health professional version. Available at: https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq. Retrieved October 22, 2019.

120. HealthDecision. Screening mammography–clinician instructions. Available at: https://www.healthdecision.org/tool.html#/tool/mammo. Retrieved October 23, 2019.

121. Ozanne EM, Annis C, Adduci K, Showstack J, Esserman L. Pilot trial of a computerized decision aid for breast cancer prevention. Breast J 2007;13:147–54.

122. Ozanne EM, Howe R, Omer Z, Esserman LJ. Development of a personalized decision aid for breast cancer risk reduction and management. BMC Med Inform Decis Mak 2014;14:4.

123. Metcalfe KA, Dennis CL, Poll A, Armel S, Demsky R, Carlsson L, et al. Effect of decision aid for breast cancer prevention on decisional conflict in women with a BRCA1 or BRCA2 mutation: a multisite, randomized, controlled trial. Genet Med 2017;19:330–6.

124. Schapira MM, Hubbard RA, Seitz HH, Conant EF, Schnall M, Cappella JN, et al. The impact of a risk-based breast cancer screening decision aid on initiation of mammography among younger women: report of a randomized trial. MDM Policy Pract 2019;4:2381468318812889.

125. Joseph G, Beattie MS, Lee R, Braithwaite D, Wilcox C, Metrikin M, et al. Pre-counseling education for low literacy women at risk of Hereditary Breast and Ovarian Cancer (HBOC): patient experiences using the Cancer Risk Education Intervention Tool (CREdIT). J Genet Couns 2010;19:447–62.

126. Doughty MJ. An applied research intervention: breast cancer and preventive services in African American women. Health Promot Pract 2013;14:732–40.

127. Volk RJ, Linder SK, Lopez-Olivo MA, Kamath GR, Reuland DS, Saraykar SS, et al. Patient decision aids for colorectal cancer screening: a systematic review and meta-analysis. Am J Prev Med 2016;51:779–91.

128. Ottawa Hospital Research Institute. Patient decision aids. Available at: https://decisionaid.ohri.ca/. Retrieved October 22, 2019.

129. McMeekin P, Flynn D, Ford GA, Rodgers H, Gray J, Thomson RG. Development of a decision analytic model to support decision making and risk communication about thrombolytic treatment [published erratum appears in BMC Med Inform Decis Mak 2016;16:4]. BMC Med Inform Decis Mak 2015;15:90.

130. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402–16.

131. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collee JM, van Doorn HC, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. Hereditary Breast and Ovarian Cancer Research Group Netherlands. J Natl Cancer Inst 2015;107:pii: djv033.

132. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.

133. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003;361:296–300.

134. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis [published erratum appears in J Natl Cancer Inst 2014;106:dju235]. J Natl Cancer Inst 2014;106:dju091.

135. Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 2010;46:2275–84.

136. Scoccianti C, Lauby-Secretan B, Bello PY, Chajes V, Romieu I. Female breast cancer and alcohol consumption: a review of the literature. Am J Prev Med 2014;46:S 16–25.

137. Harvie M, Howell A, Evans DG. Can diet and lifestyle prevent breast cancer: what is the evidence? Am Soc Clin Oncol Educ Book 2015;e66–73. Available at: https://meetinglibrary.asco.org/record/105445/edbook. Retrieved October 11, 2019.

138. National Comprehensive Cancer Network. Survivorship. Version 2.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Retrieved October 29, 2019.

139. American Society of Clinical Oncology. Prevention and survivorship. Available at: https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/survivorship/survivorship-compendium. Retrieved April 20, 2020.

140. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. CA Cancer J Clin 2016;66:43–73.

141. Management of gynecologic issues in women with breast cancer. Practice Bulletin No. 126. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:666–82.

142. Faubion SS, Larkin LC, Stuenkel CA, Bachmann GA, Chism LA, Kagan R, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause 2018;25:596–608.

143. Dominick SA, McLean MR, Whitcomb BW, Gorman JR, Mersereau JE, Bouknight JM, et al. Contraceptive practices among female cancer survivors of reproductive age. Obstet Gynecol 2015;126:498–507.

144. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep 2016;65:1–104.

145. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis. Int J Clin Exp Pathol 2014;7:6419–29.

146. Patel A, Schwarz EB. Cancer and contraception. SFP Guideline #20121. Contraception 2012;86:191–8.

147. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36:1994–2001.

148. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol 2018;36:1981–90.

149. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. Fertil Steril 2019;112:1022–33.

150. Royal College of Obstetricians and Gynaecologists. Pregnancy and breast cancer. Green–top Guideline No. 12. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_12.pdf. Retrieved October 22, 2019.

151. Valachis A, Tsali L, Pesce LL, Polyzos NP, Dimitriadis C, Tsalis K, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. Obstet Gynecol Surv 2010;65:786–93.

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Transparency in Peer Review

The Editors of *Obstetrics & Gynecology* are seeking to increase transparency around the journal's peer-review process, in line with other efforts to do so in international biomedical peer review publishing. The journal has phased in several efforts toward this goal.

- Beginning with the July 2018 issue, all published, peer-reviewed manuscripts indicate the dates of submission, revision, and acceptance.
- Manuscripts submitted on or after June 1, 2018, and published include the revision letter uploaded as supplemental digital content to the article. The revision letter includes comments from all reviewers and the Editors. Reviewer comments will remain anonymous (unless the reviewer discloses his or her identity). If the author opts in, we will also include his or her point-by-point response to the revision letter.

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