BRCA Mutations in the Young, High-Risk Female Population: Genetic Testing, Management of Prophylactic Therapies, and Implications for Plastic Surgeons

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Summary: Growing public awareness of hereditary breast cancers, notably *BRCA1* and *BRCA2*, and increasing popularity of personalized medicine have led to a greater number of young adult patients presenting for risk-reduction mastectomies and breast reconstruction. Plastic surgeons must be familiar with treatment guidelines, necessary referral patterns, and particular needs of these patients to appropriately manage their care. Genetic testing for *BRCA1* and *BRCA2* is most often reserved for patients older than the age of consent, and can be performed in the young adult population (aged 18 to 25 years) with the appropriate preemptive genetic counseling. Subsequent risk-reduction procedures are usually delayed until at least the latter end of the young adult age range, and must be considered on an individualized basis with regard for a patient's level of maturity and autonomy. Prophylactic mastectomies in young adults also can serve to aid the unique psychosocial needs of this population, although the long-term psychological and physical ramifications must be considered carefully. With the development of nipple-sparing mastectomy and improvement in reconstructive techniques, risk-reducing surgery has become more accepted in the younger population. Immediate, implant-based reconstruction is a common reconstructive technique in these patients but requires extensive discussion regarding reconstructive goals, the risk of possible complications, and long-term implications of these procedures. Comprehensive, continuous support with multispecialty counseling is necessary throughout the spectrum of care for the high-risk, young adult patient. (*Plast. Reconstr. Surg.* 141: 1341, 2018.)

Rates of prophylactic mastectomies have risen dramatically over the past several years.[1–3] The trend has included an increase in the number of bilateral prophylactic mastectomies[1] and is similarly reflected by a rise in bilateral reconstructions.[4] The surge in risk-reducing procedures can be attributed partially to genetic testing for hereditary breast and ovarian cancer syndromes, such as breast cancer–associated genes 1 and 2 (*BRCA1* and *BRCA2*). *BRCA1* and *BRCA2* are two of many breast cancer susceptibility genes such as tumor suppressor genes (*TP53*, *PTEN*)[5] and are the most common known cause of hereditary breast cancer.[6]

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BRCA1/2 mutations significantly increase the lifetime risk of developing breast cancer, approaching

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85 percent.[7,8] Notably, mutation-specific risk is higher at a younger age compared with sporadic cancers.[9] Bilateral prophylactic mastectomies have been shown to reduce the risk of breast cancer in these patients by approximately 90 percent.[10]

Public awareness of genetic predispositions to cancer[11] and precancer genetic testing and prophylactic surgery[12] has increased through mainstream and social media.[13,14] Greater availability of genetic testing,[15] a public desire for education through social media,[16] and a push for personalized genomic medicine[17,18] have further reinforced expectations for early diagnosis and comprehensive management of genetic conditions. The term "previvor," or survivor of a predisposition to cancer, has become popularized among high-risk patients and implies that diagnosis, screening, and prophylactic therapies are conducted at an appropriate time to prevent the development of cancer. Is the earlier, then, the better?

The management of genetic testing, cancer screening, and prophylactic interventions in high-risk young female adults remains controversial.[19–22] In families with hereditary disease, communication of potential risk creates a delicate scenario that raises ethical questions regarding autonomy, uncertainty, choice, and medical treatment.[23] Risk-reduction and reconstructive goals must be considered alongside psychological benefits and harms from early intervention in a population with newly developing maturity in decision-making capabilities.

Patients undergoing bilateral risk-reduction mastectomies have the highest rate of immediate breast reconstruction.[1] As earlier genetic testing for *BRCA* mutations continues, plastic surgeons will have to learn how to counsel young patients on their options for surgical treatment and the long-term implications of these surgical interventions alongside breast surgeons, oncologists, and genetic specialists. This requires an in-depth understanding of this patient population and their risk of disease.

THE *BRCA* MUTATIONS

BRCA1 and *BRCA2* are tumor suppressors[24,25] responsible for approximately 2 to 10 percent of all breast cancers,[26–28] varying by ethnic group. Breast cancer in *BRCA1* mutation carriers is more likely to be triple-negative.[29] In contrast, *BRCA2* mutations are associated with estrogen receptor–positive cancers.[30] In addition, *BRCA1/2* mutations confer a significant risk of ovarian cancer (40 percent and 18 percent, respectively),[31] and an increased but lesser risk for other secondary malignancies, including pancreatic cancer, leukemia, and lymphoma.[32,33]

Risk of Breast Cancer

It is estimated that approximately 0.2 to 0.3 percent of the general population carries either *BRCA1* or *BRCA2* mutations.[28] By age 70, the average risk of developing breast cancer is nearly 60 to 65 percent in *BRCA1* mutation carriers and 45 to 55 percent in *BRCA2* mutation carriers.[31,34,35] In *BRCA1/2*–positive patients with a known family history of breast or ovarian cancer, this risk is even higher, and can be upward of 85 to 87 percent.[7,36] The risk of developing breast cancer by age 30, however, is decreased to 3.4 percent (*BRCA1)* and 1.5 percent (*BRCA2*).[31,37] The relative risk for breast cancer in *BRCA1* and *BRCA2* mutation patients is 17 and 19 (age 20 to 29 years), 32 and 10 (age 40 to 49 years), and 14 and 11 (age 60 to 69 years), respectively.[38] However, the absolute risk is still very low for patients younger than 30 years, given the rarity of the disease at younger ages. At age 20, the risk of developing breast cancer by age 30 is 1.8 percent for *BRCA1* mutation carriers and 1 percent for *BRCA2* mutation carriers.[31]

Although lifetime and multidecade risk projections must be taken into account, the management of young female patients should also consider the shorter term risks when planning the timing of counseling, screening, and risk reduction. Although there is a much higher risk of breast cancer at an earlier age with hereditary cases, it remains an adult-onset genetic disorder. Regardless, different interventions should be thought of not only in terms of absolute risk reduction but as one part of a greater comprehensive goal in managing patients' expectations, psychosocial needs, life planning, and overall well-being.

GENETIC TESTING

Current Recommendations

Genetic testing has strong implications, as *BRCA1/2* mutations are inherited in an autosomal dominant fashion. The U.S. Preventive Services Task Force recommends genetic counseling and evaluation for hereditary breast cancer–related mutations for women with a family history associated with an increased risk for *BRCA1* and *BRCA2* genes.[39] These family history patterns of risk include different combinations of first- and second-degree relatives with known breast cancer diagnoses varying with age, ethnicity, sex, other cancers, and bilateral breast disease. Genetic testing has been suggested to improve management of these patients only if one's family history is suggestive of a likely inherited cancer.[40] Individual risk stratification based on family history is complex, and

Table 1. Important Family History Factors When Assessing Risk for Hereditary Breast Cancer*

Breast cancer diagnosed at age 45 or younger
Triple-negative breast cancer diagnosed at age 60 or younger
History of male breast cancer
History of ovarian cancer
Bilateral primary breast cancer
Breast and ovarian cancer in the same person
Ashkenazi Jewish heritage with history of breast or ovarian cancer
Risk factors present in single or multiple first- or second-degree relatives
Known *BRCA1* or *BRCA2* mutation

*Based on variables in various risk assessment calculators for hereditary breast and ovarian cancer (Centers for Disease Control and Prevention. Breast and ovarian cancer and family history risk categories. Available at: https://www.cdc.gov/genomics/resources/diseases/breast_ovarian_cancer/risk_categories.htm. Accessed October 31, 2017. Evans DG, Eccles DM, Rahman N, et al. A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO. *J Med Genet.* 2004;41:474–480. 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;11:783–789. Gilpin CA, Carson N, Hunter AG. A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. *Clin Genet.* 2000;58:299–308).

should be performed in a multidisciplinary setting with guidance from genetic counselors. Several risk-assessment tools are available for determining individual inherited cancer susceptibility, including the Centers for Disease Control and Prevention Breast and Ovarian Cancer and Family History Risk Categories,[41] the Manchester Scoring System,[42] the Breast Cancer Genetics Referral Screening Tool,[43] the Ontario Family History Assessment Tool,[44] and others. These tools take into account different historical factors to calculate overall risk scores for hereditary breast and ovarian cancer syndromes (Table 1) and can subsequently be used to determine whether in-depth genetic counseling and testing may be beneficial in a particular patient.

In addition to these criteria, the U.S. Preventive Services Task Force recommends that *BRCA* mutation screening should be considered only once women have reached the age of 18, which is the "age of consent."[45] This age recommendation is echoed by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[46] Similarly, cancer risk-assessment guidelines first published in 2004 by the National Society of Genetic Counselors[47] and subsequently updated in 2012[48] state that patients should wait until at least the age of 18 to discuss genetic testing, based on decision-making capacity in this age group. Patients' family history and age of breast cancer diagnoses in relatives should also influence the decision for earlier or later testing.

Genetic Testing in Young Adults

Although organizational recommendations have suggested a minimum age for genetic testing, age should be interpreted as a flexible criterion.[49] *BRCA* mutation testing in young adults aged 18 to 25 years remains controversial, particularly because of the psychosocial implications of testing. This age demographic has been described as "emerging adults," who are characterized by social exploration, instability, and constant evolution.[50] Independent decision-making is not fully developed at this time, and patients often arrive at decisions based on self-perceived rather than absolute risk.[51] In the case of adult-onset diseases, such as *BRCA1* and *BRCA2*–associated breast cancer, more weight is given to an individual's maturity and ability to make informed decisions and adequately process information rather than absolute age.[22,52]

Patients aged 18 to 25 years who test *BRCA* mutation–positive are in a clinical limbo, as cancer screening and any risk-reduction interventions are not recommended until age 25.[53] Critics of genetic testing in young female adults cite the very low risk of developing breast cancer at this age and potential negative psychological consequences of genetic testing. However, studies have shown that distress levels in patients who test positive trend back to baseline several months after testing, and negative test results cause a significant reduction in distress compared with pretest levels.[54] Patients who test positive may also find some relief from the burden of uncertainty, as they are able to take control of their health.[55] Furthermore, life decisions at this age can be influenced by genetic testing results, such as relationship and reproductive planning, and therefore benefit may be derived from appropriate genetic counseling based on concrete results.[56,57]

In young adult patients, pretest genetic counseling and the promotion of patient autonomy is necessary[58] to prepare patients to manage the sequelae of either positive or negative results. Perceived disadvantages of testing in young women include increased pressure to make impactful decisions about one's life and a lack of clear

screening or treatment steps after a positive diagnosis at a young age.[55] An ongoing, continuous support system during these years from genetic counselors and other providers is critical,[56,59] as the patient's autonomy and ability to make health care decisions is an evolving process during this time.[57]

Genetic Testing in Minors

Genetic testing in children is usually discouraged for adult-onset hereditary disorders. The American Academy of Pediatrics does not recommend genetic testing or screening in patients younger than 18 years unless it impacts medical management,[60] such that intervention affects morbidity/mortality or changes early treatment decision-making in patients from high-risk families. According to ethical standards, pediatric health care decisions should be made in the "best interest" of the child,[61] and presymptomatic, predictive genetic testing for *BRCA* mutation–associated breast cancer does not qualify, as this extent of early testing does not correspond to direct benefit from early intervention or prevention.[62] Genetic counseling, however, can be initiated early, and can be a powerful tool in helping to make adolescents aware of their potential carrier status to better understand their risk while preparing to manage the steps after future testing.

The decision to proceed with genetic testing in minors may occur in adolescent patients with a significant psychosocial burden from risk status who desire predictive testing themselves. It has been suggested that mature children with the capacity to comprehend the implications of predictive testing and the appropriate parental relationships may benefit from relief of uncertainty and facilitated autonomy through testing.[21,63–65] In these cases, consent should be obtained from the patient's parents/guardians along with assent from the child. Pretest genetic counseling is critical to prepare the patient for either positive or negative testing results.

Although *BRCA*-mutation predictive testing is relatively uncommon, children's awareness of their own possible risk may occur quite frequently. Parental surveys have yielded mixed results on *BRCA* testing of their children[66]; however, parents with hereditary cancer will often communicate their diagnoses with minor children.[67,68] Awareness of risk status may lead older adolescents and young adults to more actively seek out predictive testing, substantiating the need for early genetic counseling and more structured screening and interventional guidelines in this age demographic.

RISK REDUCTION

Prophylactic Mastectomy

Decisions to pursue risk-reduction interventions among young female adults are influenced by several life trajectories, including longstanding awareness of disease in family, loss of a patient's mother and/or another close relative, and concern expressed by health care providers.[69] Prophylactic surgery in *BRCA1/2*-positive patients is usually not recommended until patients are in the latter end of young adulthood (age 25 or older) at a minimum.[70] Risks of developing breast cancer by age 30 are 3.4 percent and 1.5 percent in *BRCA1* and *BRCA2* patients, respectively.[31,37] Thus, there is usually no urgency for early mastectomy, with the exception of families with cases of very early-onset cancer. However, multiple other psychosocial factors can influence patients' decisions to proceed with surgery.

Anticipatory loss, or the "possible, probable or inevitable future loss,"[71] is a heavy burden for *BRCA1/2*-positive patients.[72] Fear secondary to uncertainty of developing cancer can have a strong influence on decision-making and must be balanced with absolute risk reduction and quality of life.[73] A significant decrease in distress and anxiety and improved psychological outcomes have been demonstrated in patients after undergoing risk-reducing mastectomy.[74,75] These outcomes may often take precedence over actual risk reduction when deciding on procedural timing at a young age.[72]

In contrast, the negative physical and psychosocial consequences of mastectomies must be carefully considered for young female adults. Acceptance of body image, sexuality, interpersonal relationships, and personal responsibilities are an evolving process during the emerging adult years that can be significantly impacted by this surgery and must be treated delicately. Women who have undergone prophylactic mastectomy may have difficulty adapting to changes in sexuality and new body image.[75,76] In addition, postoperative satisfaction with one's decision to undergo prophylactic mastectomy is decreased in younger women compared with older women.[77,78] However, long-term studies have shown favorable psychosocial outcomes and decreased concern regarding cancer in patients who have undergone bilateral risk-reducing surgery.[78]

Bilateral prophylactic mastectomies reduce the risk of breast cancer in hereditary mutation carriers by nearly 90 percent.[10] Importantly, they do not completely prevent the risk of developing breast cancer. As previvors are not undergoing therapeutic surgery but oncologic risk-reducing surgery, this residual lifetime risk and the need for continued screening must be thoroughly explained to patients. Furthermore, timing of surgery must be considered in light of a patient population at an early reproductive age. Family planning is critical, as patients often experience a "compressed life cycle" because of increased pressures to have children early.[79] As surgery is often delayed until after pregnancy, these life choices affect decisions to undergo mastectomy and reconstruction. Several other nonstandard points of discussion arise for patients planning for pregnancy such as inability to breast feed and possible risks with prior abdominally based autologous breast reconstruction.[80] These choices also have significant implications for other risk-reduction therapies such as salpingo-oophorectomy.[81] As with genetic testing, the decision for prophylactic surgical intervention must be approached on a case-by-case basis to assess a patient's capacity to comprehend the risks and implications of the surgery. Similarly, genetic counseling is imperative before proceeding with a discussion of surgical interventions.

BREAST RECONSTRUCTION

High-risk patients undergoing bilateral prophylactic mastectomies have the highest rates of immediate reconstruction.[1] Multiple reconstructive procedures are feasible after prophylactic mastectomies, with implant-based and autologous techniques both demonstrating promising outcomes.[82] However, there has been a general shift toward implant-based reconstruction, particularly after bilateral prophylactic mastectomies.[1] In the very young patient, additional considerations must be taken into account during the preoperative evaluation to determine the most appropriate reconstructive paradigm.

Nipple-sparing mastectomy is the ideal mastectomy technique in many bilateral prophylactic cases, as it offers an oncologically sound removal of breast tissue[83,84] and optimizes aesthetic results. Maximal preservation of the skin envelope is key in these young patients. Patient who have undergone nipple-sparing mastectomy have improved postoperative satisfaction and body image.[85,86] The increased popularity of nipple-sparing mastectomy has accelerated the acceptance of mastectomy and subsequent reconstruction in the younger patient population. These patients may further benefit from immediate reconstruction, which has been associated with decreased psychosocial stress and fewer problems with body image and sexuality.[87,88]

With regard to reconstruction technique, autologous breast reconstruction has demonstrated good aesthetic results with high long-term satisfaction in a single-stage procedure.[89,90] However, extra scars, additional donor-site morbidity, and a lengthier operation and hospital stay might not be as accepted by a young patient population. In addition, young patients frequently are thin, making the most frequent donor site (abdomen) unavailable. In contrast, the higher rate of long-term complications and revisions with implant-based techniques must be discussed. Given the early age of implant placement, patients must understand changes over time in the breast capsule, pocket, and implant position that will almost guarantee the need for at least one revision at some point. Conversion to autologous reconstruction is a possibility later in life as donor sites potentially become available.

The process of informed consent and clear communication of risks, benefits, and long-term implications of reconstructive procedures is critical as with any preoperative discussion. This becomes a matter of importance in patients undergoing elective, prophylactic breast surgery at a young age. Assessing the patient's ability to comprehend and accept these issues is paramount and must be assessed by the counseling team, as it may dictate timing and handing of treatments initially offered. The decision-making capacity and maturity of emerging adults is an evolving process and must be treated carefully for procedures with lifelong implications. Furthermore, it can be more difficult for these patients to understand and handle postoperative complications psychologically, as they have no preoperative pathologic condition requiring excision, making the procedure, in a sense, more "elective." Studies have shown that patients undergoing mastectomy are overall poorly informed about breast reconstruction.[91,92] High-quality decision-making in breast reconstruction is critical to ensure that the treatments offered reflect the preferences of the well-informed patient.[93] Providing adequate two-way discussions with patients, maintaining seamless communication between multidisciplinary teams, using patient-centered metrics for outcomes evaluation, and using clinical decision-making

aids can help move toward ensuring educated and evidence-based decision-making by these patients.[88,93,94]

Complication rates for breast reconstruction after bilateral prophylactic mastectomies and reconstruction are comparable to rates after therapeutic mastectomy in prior studies.[82] Ischemic complications, including nipple and flap necrosis, are low[83,84,95]; however, these can be particularly devastating with full-thickness loss. These and other major complications, including explantation and reconstructive failure, must be understood by the patient. Accurately conveying the rates and implications of these complications, both major and minor, is particularly critical in the young patient population undergoing prophylactic mastectomy. The ability to work toward stratifying individual risk for particular complications[96] will help these patients choose the appropriate type and timing of reconstructive surgery.

Goals with regard to aesthetic outcomes, symmetry, and natural results must be reviewed extensively preoperatively. Studies have shown that women undergoing reconstruction after bilateral prophylactic mastectomies have problems with body image postoperatively.[74,97] Advances with nipple-sparing mastectomy, however, have led to significantly improved body image and sexuality compared with total mastectomies in bilateral risk-reduction patients.[86] Discussion of long-term risks, including capsular contracture, asymmetry, double-bubble deformity, and implant malposition, is especially relevant in this population, given the length of time patients will be living with their reconstruction. In addition, the risk of breast implant–associated anaplastic large cell lymphoma,[98,99] although rare, is important to discuss with young patients undergoing risk-reducing surgery if textured surface implants are used for the reconstruction. If the reconstruction is performed with smooth surface implants, the anaplastic large cell lymphoma discussion is not required.

Heightened public awareness of *BRCA* mutation testing and risk-reduction interventions secondary to media coverage will continue to increase the number of young, high-risk patients seen by plastic surgeons. In addition, the reconstruction and recovery process are often the most publicized in the spectrum of the care of these patients. Plastic surgeons may therefore be the first physicians to encounter these young patients and must be knowledgeable regarding their appropriate management (Table 2). Importantly, patients should be provided appropriate referrals, including to a genetic counselor and subsequently an oncologist and breast surgeon as needed. Appropriate genetic counseling on a case-by-case basis is the most important and first step toward assessing risk in these patients and subsequently creating an individualized, comprehensive plan for psychological support, screening, risk reduction, and reconstruction (Fig. 1). Given the young age of this population and the gravity of the decision to undergo surgery, with its lifelong implications, providers should also evaluate individual patients for additional psychiatric/psychological counseling to aid patients in the decision-making process. Furthermore, standardized outcomes-based research on patient satisfaction and long-term complications after breast reconstruction in this patient population is needed to

Table 2. Important Guidelines for Plastic Surgeons Caring for Young *BRCA* Mutation–Positive Patients

Preoperative consultation
Ensure patients have access to appropriate genetic and oncologic counseling
Determine patients' capacity to understand lifelong implications of mastectomy and breast reconstruction
Arrive at a mutual decision on the most appropriate reconstructive technique
Clearly discuss goals of reconstruction
Ensure patient comprehension of risks of reconstruction and possible complications (including long-term complications, such as capsular contracture, implant malposition, ALCL, and others)
Immediate postoperative follow-up
See patients as often as necessary to meet needs
Manage any possible complications quickly and attentively
Review expectations for reconstruction
Continue to build on patient-doctor rapport to establish continuous support
Long-term follow-up
Continually assess patient satisfaction
Maintain standardized data on patient and reconstruction outcomes
Regularly monitor for late-onset complications
Maintain awareness of other prophylactic/therapeutic treatments for *BRCA* mutation
Coordinate with oncologic colleagues to ensure appropriate and continued cancer surveillance
Continue to offer and sustain support as needed

ALCL, anaplastic large cell lymphoma.

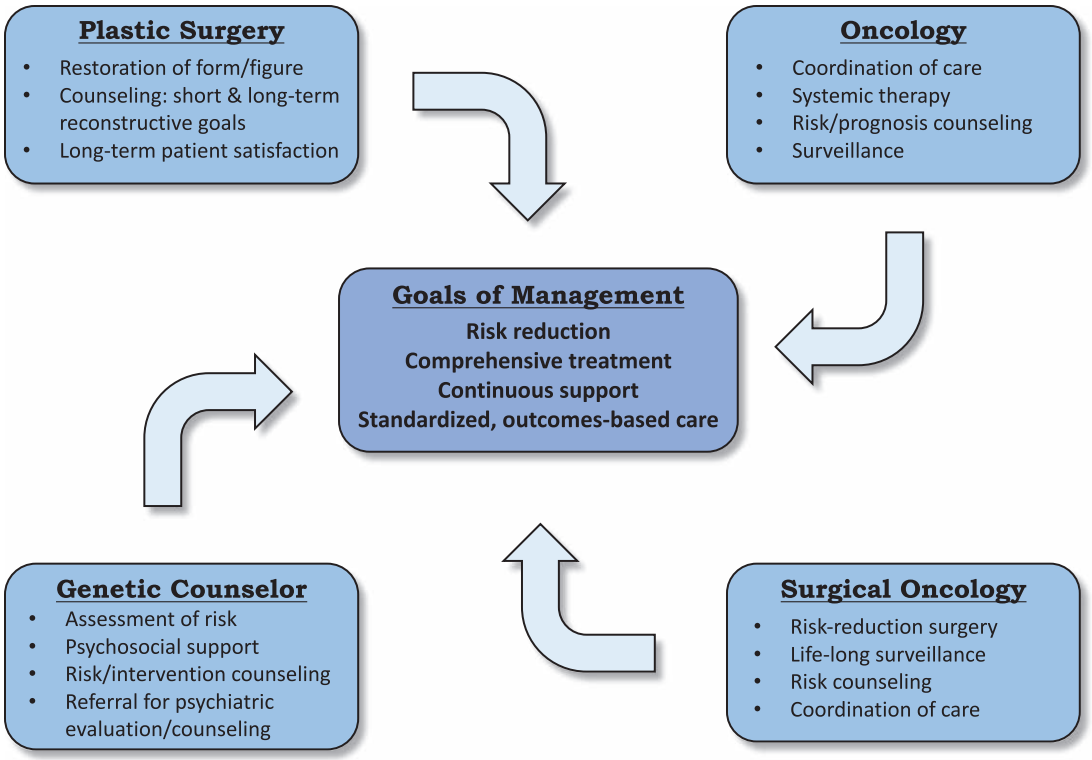

Fig. 1. Multispecialty comprehensive management of young adult female patients at high risk for breast cancer.

be able to appropriately counsel patients on their reconstructive choices.

CONCLUSIONS

Genetic testing for *BRCA1* and *BRCA2* should be delayed until at least the age of 18 years in the majority of cases. However, testing in high-risk young adult patients can be appropriate in the setting of comprehensive genetic counseling and support from health care professionals. Continuous multispecialty care with an emphasis on preemptive genetic and psychosocial counseling is critical in all cases to meet the evolving needs of the young female adult population. Risk-reduction mastectomy and subsequent reconstruction in emerging adults should be assessed on a case-by-case basis and be delayed until patients have the maturity to fully comprehend all risk and benefit implications of these procedures. It is the responsibility of the plastic surgeon to understand the basic risks of these mutations, refer patients to the appropriate providers as necessary, and alter reconstruction and counseling paradigms to fit the needs of these young patients. Further long-term, outcomes-based research is needed to standardize guidelines for management of the *BRCA*-positive young female adult population.

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