



Breast Cancer Risk Assessment: Calculating Lifetime Risk Using the Tyrer-Cuzick Model

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ABSTRACT

One size does not fit all for breast cancer screening. Early detection and prevention are most effective for those most at risk. Several United States organizations recommend offering annual screening breast magnetic resonance imaging in addition to mammography for women with > 20% lifetime risk for breast cancer using models that take extensive family history into account. The purpose of this article is to help nurse practitioners make critical decisions about breast cancer screening and referrals to genetic services for women based on their lifetime risk for breast cancer. This article reviews several software-based risk assessment models and provides instructions for using the Tyrer-Cuzick model.

Keywords: breast cancer risk assessment, clinical decision making, familial breast cancer, hereditary breast cancer, screening breast magnetic resonance imaging

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Breast cancer is the second most diagnosed cancer and the second leading cause of cancer death in women.^{1,2} The American Cancer Society (ACS) predicts 246,600 new cases of breast cancer will be diagnosed in women during 2016 with 40,890 deaths.¹ However, early detection, in conjunction with appropriate screening, can decrease

mortality associated with breast cancer.³⁻⁵ Nurse practitioners assess breast cancer risk and recommend screening for their patients in the primary care setting. Primary care providers' recommendations have a strong influence on patient adherence to screening guidelines.^{6,7} The purposes of this article are to review breast cancer screening guidelines and to

This CE learning activity is designed to augment the knowledge, skills, and attitudes of nurse practitioners and assist in their understanding of how to best identify/manage patients who are at elevated risk for breast cancer.

At the conclusion of this activity, the participant will be able to:

- Compare/Contrast Breast CA screening guidelines for average risk and women with elevated risk
- Use the Tyrer Cuzick Model to calculate lifetime risk for Breast CA
- Describe ways to identify/manage screening needs of elevated risk women

The authors, reviewers, editors, and nurse planners all report no financial relationships that would pose a conflict of interest. The authors do not present any off-label or non-FDA-approved recommendations for treatment.

This activity has been awarded 1.0 Contact Hours of which 0.0 credits are in the area of Pharmacology. The activity is valid for CE credit until November 1, 2018.

suggest an algorithm for nurse practitioners (NPs) to use when assessing breast cancer risk and making decisions about referral and breast cancer screening. Finally, this article will provide instruction for NPs to use the Tyrer-Cuzick model to calculate lifetime risk for breast cancer.

SCREENING FOR WOMEN AT AVERAGE RISK

Breast cancer screening guidelines vary by organization. The ACS updated its guidelines in October 2015 (Table 1). Key changes to the ACS guidelines are the following: 1) annual clinical breast examination is no longer recommended, 2) annual mammograms are not to begin until age 45 (however, women should have the choice to begin at age 40), and 3) at age 55 mammography should switch to every other year (women may opt for annual screening).³ The National Comprehensive Cancer Network (NCCN) and the American Congress of Obstetricians and Gynecologists still recommend clinical breast examination at least every 3 years between ages 20 and 39 years and annually from the age of 40 years on.^{8,9} These 2 organizations recommend annual mammography for all women beginning at age 40 years regardless of risk level.^{8,9} In contrast, the United States Preventive Services Task Force (USPSTF) guidelines, updated January 2016, recommend biennial screening mammography for women between ages 50 and 74 years (Table 1).¹⁰

SCREENING FOR WOMEN AT ELEVATED RISK

One size does not fit all for breast cancer screening. With the exception of the USPSTF, all of these organizations suggest more intensive screening for women with elevated risk. Although the USPSTF has not produced guidelines for women at elevated risk, it acknowledges that its guidelines are not intended for women at elevated risk.¹⁰ NPs should identify women at elevated risk and offer more intensive screening if warranted. The ACS, NCCN, and American Congress of Obstetricians and Gynecologists recommend that if a woman has $\geq 20\%$ lifetime risk for breast cancer, she should be offered an annual screening breast magnetic resonance imaging (MRI), in addition to annual mammography.^{3,8,9} The addition of breast MRI increases sensitivity in detecting breast cancer

compared with mammography alone.^{11,12} NPs may choose from a variety of models to calculate lifetime risk for breast cancer.

CALCULATING LIFETIME RISK FOR BREAST CANCER

Several software-based models can estimate a woman's lifetime risk based on family history and other risk factors. Guideline-issuing organizations recommend using only models that base risk calculations on extensive family history when determining the need for screening breast MRI.^{3,8} Some of these models include Claus, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, and the Tyrer-Cuzick.¹³⁻¹⁶ The Gail model is not appropriate to use to determine the need for breast MRI because it does not include enough family history.^{3,8}

The Tyrer-Cuzick model is a well-studied, widely available model for predicting breast cancer risk.¹⁶⁻¹⁸ This model includes the most comprehensive set of variables and is the most sensitive of all the models for detecting risk for breast cancer.^{17,19} The Tyrer-Cuzick model is the only model to account for both personal and extensive family history risk factors.¹⁶ Table 2 provides a list of personal risk factors for breast cancer and indicates which ones are included in the Tyrer-Cuzick model. Additionally, the Tyrer-Cuzick model incorporates the presence of *BRCA* gene mutations, personal risk factors, and extensive family history.^{16,19,20} In this article, instructions are provided for using the Tyrer-Cuzick model.

WHEN TO CALCULATE LIFETIME RISK FOR BREAST CANCER

Using risk-calculating models is time intensive. To use these models, NPs must collect extensive family history, often necessitating more than 1 office visit to allow patients time to collect information from extended family. It would not be feasible to calculate lifetime risk for every patient. Therefore, NPs must determine who needs more intensive risk assessment. The annual examination can be a good time to do an initial risk assessment as shown in Figure 1. NPs should regularly update and review a woman's family history and assess other risk factors for breast cancer.

Women with concerning family history and/or other risk factors may need further breast cancer risk assessment. There are no clear guidelines suggesting a

Table 1. Breast Cancer Screening Recommendations by Organization and Risk Level

Organization	Screening Recommendations for Average Risk Women				Additional Recommendations for Women With Elevated Risk
	Clinical Breast Examination	Breast Self-examination	Breast Self-awareness	Mammography	Screening Breast MRI
American Cancer Society Latest update October 2015 ³	No clear benefit	No clear benefit	Yes, be familiar with normal feeling/appearance	Annual starting at 45 (women may choose to start at 40) Every other year starting at 55 (women may choose to continue annual)	Annually starting at age 30 if lifetime risk is calculated at about 20%-25% or more by models that take extensive family history into account. At lifetime risk of 15%-20%, there is not enough evidence to recommend for or against screening breast MRI.
National Comprehensive Cancer Network Latest update 2015 ⁸	Every 1-3 years ages 25-40 Annually beginning 40	No, can be part of awareness	Yes, be familiar with normal feeling/appearance	Annually beginning at age 40	Annually starting at age 30 if lifetime risk is calculated at > 20% by models that take extensive family history into account
American Congress of Obstetricians & Gynecologists Last updated 2011, ⁹ reaffirmed 2014	Every 3 years ages 20-39 Annually beginning 40	No, can be part of awareness	Yes, be familiar with normal feeling/appearance	Annually beginning at age 40	Annually starting at age 30 if lifetime risk is calculated at \geq 20% by models that take extensive family history into account
US Preventive Services Task Force Latest update January 2016 ¹⁰	Insufficient evidence	No, recommend against teaching	No comment	Every other year ages 50-74	Does not provide recommendations for women with elevated risk

MRI = magnetic resonance imaging.

Table 2. Personal Risk Factors for Breast Cancer

Risk Factors
Advancing age ^a
Older age at first live birth (> 30 y) ^a
Younger age at menarche (< 12 y) ^a
Older age at menopause (> 55 y) ^a
Hormone replacement therapy ^a
Increased no. of breast biopsies
Increased breast density
Birth control
Radiation exposure
Decreased physical activity
Obesity
Alcohol use

Data from American Cancer Society (2015).³

^a Indicates personal risk factor taken into account by Tyrer-Cuzick model.

particular number or cluster of personal risk factors necessitating further risk assessment. However, certain family history characteristics are associated with increased risk for breast cancer. If NPs suspect women have such a family history, they should provide further assessment (Figure 1).

If a woman needs further risk assessment, NPs can either refer her to genetics professionals to receive in-depth risk evaluation and lifetime risk calculations, or NPs can perform their own calculations as part of a risk assessment (Figure 1). If NPs prefer not to perform their own risk calculations, they may choose to look at guidelines listing concerning family history characteristics^{21,22} (see [Supplementary 1](#) “Indicators for Referral,” available online at <http://www.npjjournal.org>) or use a brief screening tool to identify women appropriate for referral²³ (see [Supplementary 2](#) “Brief Screening Tools,” available online at <http://www.npjjournal.org>). Alternatively, with adequate education, NPs can use risk-calculating software, such as the Tyrer-Cuzick model, to identify women at $\geq 20\%$ lifetime risk and order a breast screening MRI if indicated. There are benefits of NPs performing their own risk calculations as opposed to using brief screening tools. The brief screening tools may miss at-risk women; alternatively, they may refer low-risk women (D.O. Himes, personal communication, August 2016). If NPs perform their

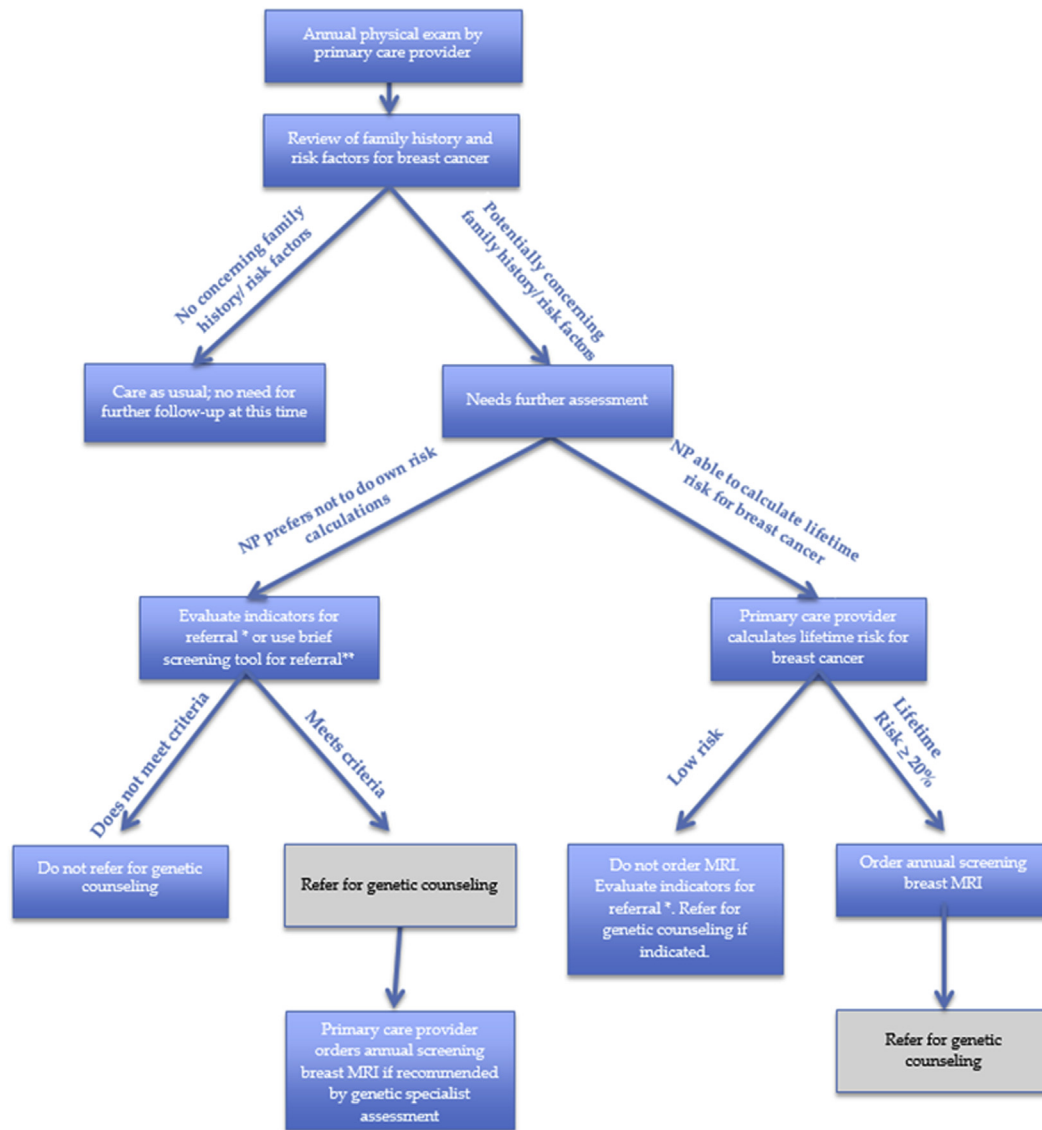
own calculations, it is helpful for women to receive earlier risk assessment without going to an additional appointment. Not everyone referred for genetic counseling attends and receives a risk assessment. Therefore, it may be advantageous to patients when NPs calculate lifetime risk for breast cancer.

USING THE TYRER-CUZICK MODEL TO CALCULATE LIFETIME RISK FOR BREAST CANCER

The Tyrer-Cuzick model is not difficult to use. A brief explanation of the steps and the order in which they should be completed are as follows:

1. Step 1: download. Free software is available for PC computers only at <http://www.ems-trials.org/riskevaluator/>.
2. Step 2: begin. Click “evaluate” and then enter the name and identification number for the consultand (Figure 2). A consultand is a person for whom the provider is performing a risk calculation. This person is identified on the pedigree with an arrow.
3. Step 3: enter personal factors. Enter the consultand’s age, age at menarche, and height and weight measurements (Figure 3). There is an option to convert the measurements of height and weight from metric into imperial terms (inches, pounds). Next, enter parity and then history of breast disease in the consultand. If the consultand has never been diagnosed with any breast abnormalities, mark the no benign disease box. If she has been diagnosed with hyperplasia, unknown benign disease, atypical hyperplasia, lobular carcinoma in situ, or ovarian cancer, mark those boxes. NPs may need to get biopsy records to confirm diagnoses. Next, enter the consultand’s menopausal status. If she had surgical menopause, enter the age she was at the time of surgery in the “age at menopause” box. The final series of questions in the personal factors section are related to hormone therapy (HRT). NPs will need to enter data about the total length of time HRT was used, how long it has been since last used, and whether estrogen only or combined (estrogen plus progesterone) therapy was used. If the woman is currently using HRT, a box will ask for intended length

Figure 1. Algorithm for assessing breast cancer risk: making decisions about referral to genetic services and ordering breast MRI screening for women.



*Indicators for referral: joint guidelines published by the American College of Medical Genetics and the National Society of Genetic Counselors as well guidelines published by the NCCN provide lists of family history characteristics appropriate for referral to genetic specialist (see supplemental material "Indicators for Referral"). **Brief screening tool for referral: the USPSTF has recommended 5 tools to evaluate family history for the purpose of referral to genetic services (see supplemental material "Brief Screening Tools").

of use. Finally, if the patient is of Ashkenazi Jewish heritage (Eastern European Jewish), mark the corresponding box because this population is at increased risk for carrying mutations in the *BRCA1* and *BRCA2* genes. The final task in the personal information section is to check the competing mortality box. Always check this box. With this box

marked, the calculations will include the possibility that someone might die from causes other than cancer before a breast cancer could manifest. Leaving this box unchecked will result in a higher lifetime risk calculation.

4. Step 4: family history; the most detailed sections of the Tyrer-Cuzick model involve entering family history. As each step is

Figure 2. Name and identification number.

The screenshot shows the 'IBIS Risk Evaluator' software interface. The 'Personal factors' section is highlighted with a blue box. Within this section, the 'Patient id. no.' field is also highlighted with a blue box. The interface includes various input fields for personal and family history, a pedigree drawing, and a 'Calculate Risk' button.

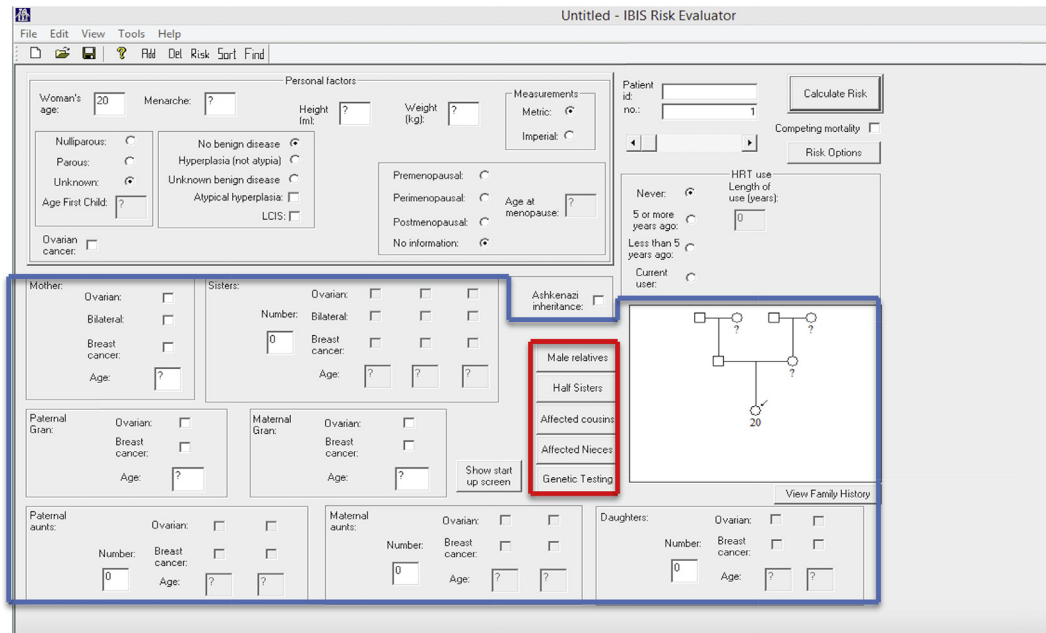
completed, a pedigree drawing on the right side will expand (Figure 4). An arrow on the pedigree indicates which family member is the consultand. The order in which this section is completed matters. Clicking the buttons to the

left of the pedigree (see red box in Figure 4) should be done last. The pop-up windows generated by clicking these buttons will vary depending on what has been entered in the previous portions of the family history.

Figure 3. Personal factors.

The screenshot shows the 'IBIS Risk Evaluator' software interface. The 'Personal factors' section is highlighted with a blue box. The interface includes various input fields for personal and family history, a pedigree drawing, and a 'Calculate Risk' button.

Figure 4. Family history; click buttons in red box last.



The overall objective with the family history section is to include family history that would influence the woman’s risk for breast cancer. All relatives and all conditions will not be included. For sisters, aunts, and daughters, the number of women in each category will need to be entered before their cancer history. The program will accept cancer history for up to 5 relatives in each of these categories. Because not all relatives can be included, NPs should preferentially choose to include relatives with cancer to account for the family risk.

Once the number of first- or second-degree female relatives is entered, NPs will need to enter current age or age of death for mother, sisters, grandmothers, aunts, and daughters. If any of these women have had ovarian, bilateral breast cancer, or breast cancer, mark those boxes, and enter the age of cancer onset rather than current age or age of death. If a woman has had either bilateral breast cancer or 2 primary breast cancers in the same breast, the “bilateral” box should be checked to account for the risk where that option is available.

After the initial family history has been completed, systematically click the buttons outlined in red (Figure 4). The first button to click is male relatives. If consultand’s brother or father has had

breast cancer, check the box, and enter age at breast cancer diagnosis. Next is a button for half sisters. The NP can record up to 2 paternal and 2 maternal half sisters. Check the breast cancer box if they have had breast cancer, and enter age of onset; if they have not had breast cancer, enter current age. Clicking the “affected cousins” button will open a pop-up window titled “cousin data” (Figure 5). Some information will already be entered based on previous information given.

The model only allows for children of up to 2 aunts and 1 uncle to be entered as affected on each side of the family. Preferentially enter aunts with children (consultand’s cousins) who have cancer. Version 7 of the IBIS Risk Evaluator software will also allow for ovarian cancer to be accounted for in this section.

Next, click the “affected nieces” button. A pop-up window titled “niece data” will open (Figure 6). The model will only allow for affected daughters of 3 sisters (consultand’s nieces) and 1 brother to be entered. If none are affected, no additional information is necessary to be entered in this section.

The last of the buttons in this section is the “genetic testing” button. Clicking this button brings up the pop-up box titled “genetic testing results”

Figure 5. Cousin data.

seen in Figure 7. Here, NPs will enter genetic test results, if available, for the consultand, paternal and maternal grandmothers, paternal and maternal aunts, father, sisters, mother, and daughters. The Tyrer-Cuzick model only accepts test results to be entered for 2 paternal and 2 maternal aunts, 3 sisters, and 2 daughters. Preferentially enter information for women affected with breast cancer. If no test has been performed, check no test. If testing has been completed and it was negative, check negative. If the consultand or family member is positive for *BRCA1* or *BRCA2* gene mutations, mark those respectively.

5. Step 5: calculating risk; after entering in all necessary information, click the calculate risk button in the upper right corner of the main screen. The consultand's level of risk will be displayed in a graph and percent format similar to Figure 8. Multiple calculations are provided. NPs will see a lifetime risk calculation, as well

as a 10-year risk. If NPs would like to see a risk level for an amount of years other than 10, a different number can be entered by clicking the "risk options" button in the upper right corner. The software provides a comparison of the consultand's risk of having breast cancer with the general population risk. The number to focus on for ordering screening breast MRI is the lifetime risk calculation. This final screen will also provide the consultand's risk of having the *BRCA1* and *BRCA2* gene mutations. If the consultand's personal risk level for a mutation is $\geq 10\%$, consider referral for genetic testing.²⁴

LIMITATIONS OF BREAST CANCER RISK ASSESSMENT

Breast cancer risk assessment can be a moving target. Updates to risk assessment models and guidelines are actively being explored. Adding risk factors such as

Figure 6. Niece data.

The screenshot shows a window titled "Niece data" with a close button (X) in the top right corner. Below the title bar is an "OK" button. The form contains several input fields and checkboxes:

- Number of sisters:** A text box containing the number "4".
- Sister 1:** A checkbox (unchecked) and a text box containing "17".
- Sister 2:** A checkbox (unchecked) and a text box containing "20".
- Sister 3:** A checkbox (unchecked) and a text box containing "25".
- Brother:** A text box containing "0".
- Number of daughters with breast cancer:** A text box containing "0".
- Ages affected:** Four text boxes, each containing a question mark "?", corresponding to the four categories above.

breast density²⁵ and single nucleotide polymorphism genetic testing panel data to risk models are being considered to further refine risk calculations. Additionally, although guidelines are currently based on lifetime risk, emerging literature suggests a move to a 10-year risk window may provide more consistency between models and would allow for more large-scale validation studies.²⁶

There are some limitations in using the Tyrer-Cuzick model in particular. This model accounts only for hereditary breast and ovarian cancer (HBOC), the most common of the hereditary breast cancer syndromes. HBOC is caused by a mutation in the *BRCA1* and *BRCA2* genes.²⁷ Many other hereditary breast cancer syndromes exist that increase a woman's risk of developing breast cancer. These syndromes and their affected genes include TP53 mutations in Li-Fraumeni syndrome, PTEN mutations in Cowden syndrome, STK11 mutations in Peutz-Jeghers syndrome, and CDH1 in hereditary diffuse gastric cancer.²⁸ More can be read about these syndromes at the Genetics Home Reference website published by the National Institutes of Health. If a woman presents with any of these syndromes, a

genetic counselor should be consulted, regardless of Tyrer-Cuzick calculation.

The Tyrer-Cuzick model cannot account for other concerning family history. According to the NCCN, women should be referred to a genetic counselor if they have a family history of 3 or more of the following: "breast, pancreatic cancer, prostate cancer (Gleason score ≥ 7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of the GI [gastrointestinal] tract."²⁹

MANAGEMENT OF WOMEN WITH ELEVATED RISK

If a woman's lifetime risk is $\geq 20\%$, annual screening breast MRI should be considered.⁸ Breast MRI should be offered in addition to annual breast mammography because mammography may detect some breast cancers missed by MRI.³ Pros and cons of annual MRI screening need to be a part of the discussion. Although MRI increases sensitivity for identifying breast cancer in high-risk women, there is also risk of false positives, which could lead to

Figure 7. Genetic testing results.

The screenshot shows a window titled "Genetic testing results" with an "OK" button in the top right corner. The window contains a pedigree chart with the following testing options for each individual:

- Individual:** No test: , Negative: , BRCA1: , BRCA2:
- Paternal gran:** No test: , Negative: , BRCA1: , BRCA2:
- Maternal gran:** No test: , Negative: , BRCA1: , BRCA2:
- Paternal aunts:**
 - Paternal aunt 1: No test: , Negative: , BRCA1: , BRCA2:
 - Paternal aunt 2: No test: , Negative: , BRCA1: , BRCA2:
- Maternal aunts:**
 - Maternal aunt 1: No test: , Negative: , BRCA1: , BRCA2:
 - Maternal aunt 2: No test: , Negative: , BRCA1: , BRCA2:
- Father:** No test: , Negative: , BRCA1: , BRCA2:
- Sisters:**
 - Sister 1: No test: , Negative: , BRCA1: , BRCA2:
 - Sister 2: No test: , Negative: , BRCA1: , BRCA2:
 - Sister 3: No test: , Negative: , BRCA1: , BRCA2:
- Mother:** No test: , Negative: , BRCA1: , BRCA2:
- Daughters:**
 - Daughter 1: No test: , Negative: , BRCA1: , BRCA2:
 - Daughter 2: No test: , Negative: , BRCA1: , BRCA2:

unnecessary biopsies. Cost is also a factor. Although mammograms are covered as preventative services by most plans (covered at 100% regardless of unmet deductible), breast MRI is not. Documentation of lifetime risk calculations will increase the likelihood of having MRI covered.

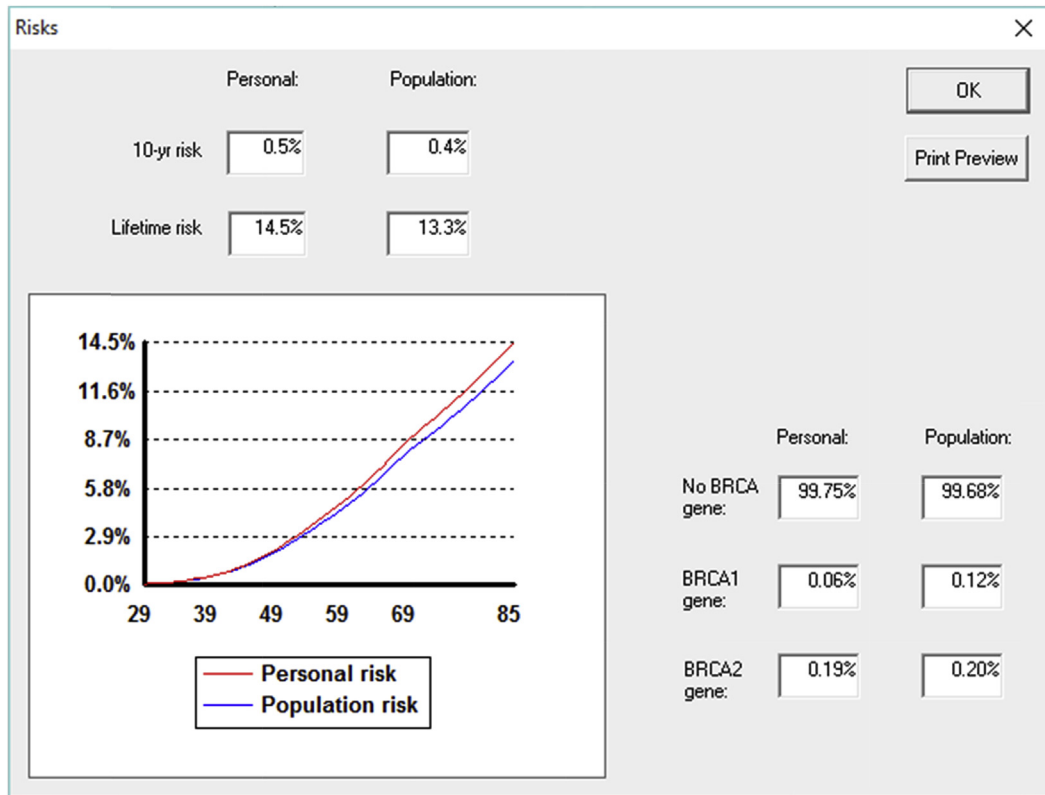
Because management of these women can be complex, interdisciplinary management is recommended. The NCCN recommends that primary care providers refer patients with elevated lifetime risk calculations $> 20\%$ for genetic counseling (Figure 1). Genetic counselors and medical geneticists are trained to evaluate pedigrees and assess for which gene mutations to test. Although mutations in *BRCA1* and *BRCA2* account for most hereditary breast cancer syndromes, many others exist. If patients are found to carry an autosomal dominant gene mutation, special follow-up is required. However, even if no mutation is identified, patients may be considered high risk based on family history alone. NCCN guidelines suggest that women with a lifetime risk $> 20\%$, as defined by assessment models that take extensive family history into account (such as the

Tyrer-Cuzick model), should receive the following beginning 10 years before the onset of cancer in the family: annual screening mammogram, annual breast MRI (alternate every 6 months), clinical breast examination every 6 to 12 months, and participation in breast awareness.⁸

It is important to note that calculating lifetime risk is not the only component of a risk assessment and ordering screening breast MRI is not the only prevention/surveillance intervention for women at elevated risk. In addition to screening breast MRI, women with elevated risk also benefit from risk reduction strategies including lifestyle modifications and chemoprevention.³⁰ It is beyond the scope of this article to describe all appropriate interventions for women at elevated risk.

Women should have their breast cancer risk reassessed periodically. A woman's remaining lifetime risk for breast cancer changes over time. Although she may have a risk over 20% at age 35, risk may not be as high at age 60 because she has lived through more of her lifetime risk. Additionally, if other cancers are diagnosed in the family or if genetic

Figure 8. Risks.



mutations are identified, risk may increase. Therefore, risk assessment is not a 1-time event.

BILLING

The USPSTF has determined the screening and referral of women to genetic services for counseling and testing if appropriate is a level B recommendation, meaning there is sufficient evidence to recommend the service. According to the Affordable Care Act, preventive measures rated level A or B by the USPSTF must be covered without copayment by the patient.³¹ Therefore, if primary care providers determine patients need referral to genetic counselors, the services should be covered by insurance.

Consulting with patients about breast cancer risk is reimbursable if the NP uses the appropriate *International Statistical Classification of Diseases, 10th Revision (ICD-10)* and *Current Procedural Terminology* codes. Potential *ICD-10* codes eligible for reimbursement include Z31.5 (encounter for genetic counseling),

Z15.01 (encounter for genetic counseling [Z15.01 is not a principal or first-listed code; it may be used in conjunction with Z31.5. If used together, Z31.5 must be listed first]), Z80.3 (family history of malignant neoplasm of breast), and Z80.41 (family history of malignant neoplasm of ovary). However, the *ICD-10* code must be billed in conjunction with a 96040 (medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family) *Current Procedural Terminology* code.³²

CONCLUSION

Women at elevated risk for breast cancer rarely receive screening breast MRI as recommended by several US guidelines. It may be that many clinicians are not familiar with or do not use risk-calculating software. This article reviewed current guidelines regarding breast MRI and instructions for use of the most accessible and comprehensive risk calculation model. Furthermore, this article suggested an algorithm for NPs to use when assessing breast cancer risk

and making decisions about referral and breast cancer screening. However, risk assessment and any individual's breast cancer risk are moving targets. This is a rapidly changing field, and tools and guidelines will continue to change. Therefore, practitioners need to stay abreast of new developments.

SUPPLEMENTARY DATA

Supplementary tables associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.nurpra.2016.07.027>. **JNP**

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