

Breast cancer risk assessment: Evaluation of screening tools for genetics referral

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ABSTRACT

Background and purpose: The United States Preventative Services Task Force (USPSTF) recommends breast cancer risk-screening tools to help primary care providers determine which unaffected patients to refer to genetic specialists. The USPSTF does not recommend one tool above others. The purpose of this study was to compare tool performance in identifying women at risk for breast cancer.

Methods: Pedigrees of 85 women aged 40–74 years with first-degree female relative with breast cancer were evaluated using five tools: Family History Screen-7 (FHS-7), Pedigree Assessment Tool, Manchester Scoring System, Referral Screening Tool, and Ontario Family History Assessment Tool (Ontario-FHAT). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to describe each tool's ability to identify women with elevated risk as defined by Claus Model calculations (lifetime risk $\geq 15\%$). Receiver operating curves were plotted. Differences between areas under the curve were estimated and compared through logistic regression to assess for differences in tool performance.

Conclusions: Claus calculations identified 14 of 85 women with elevated risk. Two tools, Ontario-FHAT and FHS-7, identified all women with elevated risk (sensitivity 100%). The FHS-7 tool flagged all participants (specificity 0%). The Ontario-FHAT flagged 59 participants as needing referral (specificity 36.2%) and had a NPV of 100%. Area under the curve values were not significantly different between tools (all p values $> .05$), and thus were not helpful in discriminating between the tools.

Implications for practice: The Ontario-FHAT outperformed other tools in sensitivity and NPV; however, low specificity and PPV must be balanced against these findings. Thus, the Ontario-FHAT can help determine which women would benefit from referral to genetics specialists.

Keywords: *BRCA1*; *BRCA2*; *BRCA1/2*; breast cancer risk assessment; familial breast cancer; FHS-7; genetic referral; genetic risk for breast cancer; HBOC; hereditary breast cancer; Manchester Scoring System; medical management; Ontario-FHAT; PAT; RST; USPSTF guidelines.

Journal of the American Association of Nurse Practitioners 31 (2019) 562–572, © 2019 American Association of Nurse Practitioners

DOI# 10.1097/JXX.0000000000000272

Introduction

The United States Preventative Services Task Force (USPSTF) recommends that asymptomatic women who have not been diagnosed with breast cancer but who have concerning family history, including family members with breast cancer, be assessed for cancer risk (Moyer, 2014). Although some clinicians may be skilled at

performing in-depth risk assessments, others may opt to refer patients to genetics specialists for assessment. Therefore, to help clinicians identify patients who need referral, the USPSTF recommended primary care providers (PCPs) screen women by applying one of five screening tools (Moyer, 2014). The screening tools are designed to identify women who may have greater likelihood of developing breast cancer (Moyer, 2014). The USPSTF did not identify which tool is best for identifying patients needing referral (Moyer, 2014).

Background

The burden of breast cancer is significant. Breast cancer is the most common cancer in women second only to skin cancer (American Cancer Society, 2019). In 2019 in the United States, it is estimated that 268,600 women will be

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Received: 26 February 2019; **revised:** 30 May 2019; **accepted:** 6 June 2019

newly diagnosed with breast cancer (American Cancer Society, 2019). The 2017 cost of breast cancer care in the United States was estimated at 147.3 billion dollars (National Cancer Institute, 2018).

Guidelines for breast cancer screening vary based on individual risk. Because age of initiation, type, and frequency of screening varies, identifying women at elevated risk for breast cancer is essential to recommending appropriate screening. Women at increased breast cancer risk may be offered earlier, more extensive screenings including magnetic resonance imaging (MRI) MRIs in addition to annual mammograms depending on family history beginning at age 30 years or earlier (National Comprehensive Cancer Network, 2018; Saslow et al., 2007). In addition, USPSTF recommends for women with *BRCA1/2* mutations, prophylactic mastectomies, and preventative chemotherapeutic medications to reduce breast cancer risk (Moyer, 2014). Therefore, if individual risk is not calculated, women may not receive appropriate type and frequency of screening and other risk reduction treatments.

Multiple risk assessment models are available to calculate lifetime risk for breast cancer; some of these include BRCAPRO, Claus, Tyrer-Cuzick, and BOADICEA (Table 1). Models may estimate breast cancer risk differently because they include different risk factors or weigh risk factors differently (National Cancer Institute, 2019; Ozanne et al., 2013). Some risk models use only pedigree analysis, whereas other models include additional breast cancer risk factors such as early menarche or delayed childbearing. Only risk models that include extensive family history should be used for recommending annual breast screening MRI (NCCN, 2018; Saslow et al., 2007). See Table 1 for risk assessment models that use extensive family history. For this reason, the Gail Model (Gail et al., 1989), also known as the Breast Cancer Risk Assessment Tool, should not be used for determining need for screening MRI because it uses limited family history (NCCN, 2018; Saslow et al., 2007).

Use of risk assessment models can be complex. During an office visit, a PCP may not have the time to calculate breast cancer lifetime risk. Additionally, models available require specialized software and clinical time to enter data (Himes, Root, Gammon, & Luthy, 2016). Because PCPs may lack the time or expertise to calculate breast cancer lifetime risk (Hampel, Bennett, Buchanan, Pearlman, & Wiesner, 2015), the USPSTF has recommended five screening tools (Moyer, 2014) to identify patients who would benefit from referral to genetics professionals for in-depth risk assessment (Table 1). The USPSTF did not identify which tool is superior. Therefore, the purpose of this study was to assess the effectiveness of five tools recommended by the USPSTF in identifying women at elevated breast cancer risk. Use of these tools will then allow guideline-

Table 1. Description and examples of risk models versus screening tools

Description	Examples
Risk assessment models ^a : Used as part of an in-depth risk assessment for hereditary cancer syndromes and/or likelihood of carrying <i>BRCA1/2</i> mutations. Requires specialized computer software. Models take extensive family history into account. Used to calculate risk for breast cancer (as % in number of years or lifetime). Appropriate to use for purpose of determining who to offer breast MRI as part of annual screening.	BRCAPRO ^b Claus ^c Tyrer-Cuzick ^d BOADICEA ^e
Screening tools to guide referral: Designed to assist primary care providers identify women who would benefit from referral to genetics specialists for in-depth risk assessment. Paper/pencil instruments that require just a few minutes of time. These tools provide a general assessment of breast cancer risk and/or likelihood of carrying <i>BRCA1/2</i> mutation. These are NOT to be used for the purpose of determining who to offer breast MRI as part of annual screening.	Ontario-FHAT ^f Manchester ^g RST ^h FHS-7 ⁱ PAT ^j

Note: MRI = magnetic resonance imaging; PAT = Pedigree Assessment Tool; RST = Referral Screening Tool.
^aNote, although the Gail Model (Breast Cancer Risk Assessment Tool—BCRAT) will also calculate lifetime and 5-year risk, it is not recommended for use in determining who should be offered screening breast MRI because it does not take extensive family history into account.
^bBerry et al. (2002).
^cClaus et al. (1994).
^dTyrer, Duffy, & Cuzick (2004).
^eAntoniou, Cunningham, et al. (2008).
^fFamily History Assessment Tool (FHAT), also called Ontario Family History Assessment Tool (Ontario-FHAT) (Gilpin et al., 2000).
^gManchester Scoring System (Evans et al., 2004).
^hReferral Screening Tool (Bellcross et al., 2009).
ⁱFamily History Screen-7 (Ashton-Prolla et al., 2009).
^jPedigree Assessment Tool (Hoskins et al., 2006).

based referral for risk assessment and, if appropriate, genetic mutation testing (NCCN, 2018).

Methods

This descriptive study used data from previous research (Himes et al., 2016). We evaluated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and receiver operating characteristic curves (ROC curve) for five screening tools. Data related to family history and risks for breast cancer were collected from 85 women through written surveys and telephone interviews.

Institutional review board approval was obtained for the original research, and all participants gave informed consent (Himes et al., 2016). Institutional review board approval was obtained separately for this study.

Participants

Participants included 85 women between the ages of 40 and 74 years. All participants were sisters or daughters of women who had a personal history of breast cancer and who had received uninformative negative genetic testing for *BRCA1/2* gene mutations results from a board-certified genetic counselor (Himes et al., 2016). Women were excluded if they had received breast cancer–related genetic testing, had received a prophylactic bilateral mastectomy or oophorectomy, had a personal history of any type of cancer other than non-melanoma skin cancer, and/or if they were of Ashkenazi Jewish descent, as the associated high-risk status with this ancestry necessitates special consideration in evaluating risk.

Measurement

Risk for breast cancer was assessed using the Claus Model and five other screening tools. The Claus Model was used as the standard against which the five screening tools were evaluated. Screening tools were considered effective if they could identify women with Claus lifetime risk $\geq 15\%$ as needing referral to a genetics professional.

Claus Model. Lifetime risk for breast cancer was calculated for 85 study participants using the Claus Model (Claus, Risch, & Thompson, 1994) as part of the parent study (Himes et al., 2016). The Claus Model is known to be moderate in its risk projections when compared with other risk assessment models (Ozanne et al., 2013). Additionally, both the NCCN (2018) and the ACS (Saslow et al., 2007) recommend the Claus Model as appropriate for calculation of breast cancer lifetime risk for the purpose of ordering breast MRI.

The Claus Model uses family history of first- and second-degree relatives with breast and ovarian cancer to estimate lifetime risk (up to age 79 years) of breast cancer (Amir, Freedman, Seruga, & Evans, 2010). The model includes information regarding age at disease onset and cancer history from both paternal and maternal family lines (Claus et al., 1994).

For the purpose of this study, women with a Claus breast cancer lifetime risk estimate of $\geq 15\%$ were considered to be at elevated risk—in other words, we counted screening tools as appropriately referring women if their lifetime risk calculation was $\geq 15\%$. Although 20% lifetime risk is the cut point at which several breast cancer screening guidelines begin to recommend MRI, we selected 15% as a cut point for three reasons. First, overreferral is preferable to underreferral in a screening test (Warner, 2004). If 20%

were the threshold, fewer women would be identified as needing referral; however, some would be missed who could benefit from risk assessment. Second, women with risks calculated in the 15–20% range may not actually be overreferred. In fact, both the American Cancer Society (2015) and the NCCN (2018) have insufficient evidence to recommend for or against screening breast MRI in women with lifetime risks between 15% and 20%. Finally, the Claus Model provides lower risk calculations than some other commonly used risk assessment models (Ozanne, 2013). Therefore, setting $\geq 15\%$ lifetime breast cancer risk as a cut point for referral recognizes that women not at elevated risk by the Claus Model could be found to be at elevated risk by other models. Thus, a 15% cut point provides a reasonable buffer allowing for variance between risk assessment models (Ozanne, 2013).

Screening tools to guide referral. The five tools in this study were recommended by the USPSTF as primary screening tools to identify patients at increased risk for breast cancer due to family history (Moyer, 2014). The recommended tools include the Family History Assessment Tool (FHAT), also known as Ontario Family History Assessment Tool (Ontario-FHAT) (Gilpin, Carson, & Hunter, 2000). In this article, we will refer to this tool as Ontario-FHAT. The other four tools include the Manchester Scoring System (Evans et al., 2004); the Referral Screening Tool (Bellcross, Lemke, Pape, Tess, & Meisner, 2009); the Family History Screen-7 (FHS-7) (Ashton-Prolla et al., 2009); and the Pedigree Assessment Tool (Hoskins, Zwaagstra, & Ranz, 2006).

All tools rely on patient knowledge of family history. Accurate recall and knowledge of cancer history to second- or third-degree relatives is key. Each tool can be completed with paper and pencil, and each takes 5 minutes or less to perform and score. An understanding of how to read pedigrees is essential. Clinicians should refer to specific instructions regarding scoring and interpreting results of each tool (original instructions are footnoted in Table 2).

Initially, each tool was developed and validated in populations of differing risk (Table 2). Validation used in-depth risk assessment models and other methods of assessing breast cancer risk and/or likelihood of *BRCA1/2* mutations rather than assessing their ability to predict breast cancer, which may occur many years into the future. See Table 2 for tool description, initial validation studies, validating population, and the gold standard measure against which it was assessed.

Procedures. For this secondary analysis, 85 de-identified participant pedigrees and Claus calculations from the parent study were accessed. Each pedigree was evaluated using all five screening tools recommended by the USPSTF. Scores derived from each instrument were compared with the participant's lifetime risk as

Table 2. Description and original validation of five screening tools

Tool Name and Description	Original Validation Studies	Original Validation Studies
<p>FHAT-Ontario^a</p> <p>No. questions: 17</p> <p>Referral cut point: ≥ 10</p> <p>May use in Ashkenazi Jewish population? Yes</p> <p>Weighted questions? No</p> <p>Note: maternal and paternal lines scored separately, highest number used to estimate risk</p>	<p>Sample:</p> <p>Purposive sample, 184 participants (all with approximately doubled lifetime risk due to family history) recruited through Ontario cancer registry, physician referrals, and a NIH local research study.</p> <p>Evaluated:</p> <p>Tool's ability to identify women who had a 22% lifetime risk for breast cancer in either the Claus Model or BRCAPRO.</p>	<p>Results: Compared with Claus Model</p> <p>Sensitivity: 0.74</p> <p>Specificity: 0.54</p> <p>PPV: 0.28</p> <p>NPV: 0.90</p> <p>AUC: not done.</p> <p>See author's original work for other comparisons</p>
<p>Manchester^b</p> <p>No. questions: 12</p> <p>Referral cut point (2 ways to score): ≥ 10 or 15</p> <p>May use in Ashkenazi Jewish population? No</p> <p>Weighted questions? Yes</p> <p>Note: Screens for both <i>BRCA1</i> and <i>BRCA2</i> mutations individually and together</p>	<p>Sample:</p> <p>Convenience sample of 422 patients with a personal or family history of breast or ovarian cancer who presented to cancer genetics clinics^b</p> <p>Those of Ashkenazi heritage excluded from sample as high risk</p> <p>Evaluated:</p> <p>Tool's ability to identify women who had a $\geq 10\%$ likelihood of carrying a <i>BRCA1/2</i> gene mutation as defined by several models/tools (BRCAPRO, Couch, Frank1, Frank 2)</p>	<p>Results: Compared with BRCAPRO</p> <p>Sensitivity: 61%</p> <p>Specificity: 44%</p> <p>AUC: 0.60</p> <p>See author's original work for other comparisons</p>
<p>RST^c</p> <p>No. questions: 18</p> <p>Referral cut point: ≥ 2</p> <p>May use in Ashkenazi Jewish population? Yes</p> <p>Weighted questions? Yes</p>	<p>Sample:</p> <p>Convenience sample of 2,464 women undergoing screening mammography.</p> <p>Evaluated:</p> <p>Tool's ability to identify women with a $\geq 10\%$ likelihood of carrying <i>BRCA1/2</i> mutation as defined by several models/tools (BOADICEA, BRCAPRO, Myriad II) or an Ontario-FHAT score ≥ 10</p>	<p>Results: Compared with BOADICEA</p> <p>Sensitivity: 0.91</p> <p>Specificity: 0.76</p> <p>AUC: 0.84</p> <p>See author's original work for other comparisons</p>

(continued)

Table 2. Description and original validation of five screening tools, continued

Tool Name and Description	Original Validation Studies	
FHS-7 ^d No. questions: 7 Referral cut point: ≥ 1 May use in Ashkenazi Jewish population? Yes Weighted questions? No	Sample: Convenience sample of 1795 women to whom FHS-7 was applied during routine visits to primary care in southern Brazil. Evaluated: Tool's ability to identify women with family history consistent with high-risk hereditary breast cancer syndromes. This included several hereditary breast cancer syndromes.	Results: Compared with women who meet clinical criteria for hereditary breast cancer syndromes (overall) Sensitivity: 0.88 Specificity: 0.56 AUC: 0.83 See author's original work for other comparisons
PAT ^e No. questions: 5 Referral cut point: ≥ 8 May use in Ashkenazi Jewish population? Yes Weighted questions? Yes Note: maternal and paternal lines scored separately, highest number used to estimate risk	Sample: Convenience sample of 3,906 women presenting at community hospital for screening mammography. Evaluated: Tool's ability to categorize women as "high BRCA probability" vs. "low BRCA probability" as defined by criteria developed by authors. AUC for tool's ability to identify women with >10% risk of carrying BRCA1/2 mutations as defined by the Frank model.	Results: Compared with criteria developed by authors Sensitivity: 100% Specificity: 93% Compared with Frank model AUC: 0.96 See author's original work for other comparisons

Note: AUC = Area under the curve; Ontario-FHAT = Ontario Family History Assessment Tool; NPV = negative predictive value; PAT = Pedigree Assessment Tool; PPV = positive predictive value; RST = Referral Screening Tool.

^aFamily History Assessment Tool, also called Ontario Family History Assessment Tool (Gilpin et al., 2000).

^bManchester Scoring System (Evans et al., 2004).

^cReferral Screening Tool (Bellcross et al., 2009).

^dFamily History Screen-7 (Ashton-Prolla et al., 2009).

^ePedigree Assessment Tool (Hoskins et al., 2006).

previously calculated by the Claus Model to determine each tool's ability to identify women with $\geq 15\%$ breast cancer lifetime risk. Women with $\geq 15\%$ risk as identified in the parent study formed the "elevated risk" group in this secondary analysis.

Data analysis

Demographic data were described using mean values, standard deviations, and percent as obtained through SPSS software version 22. Sensitivity and specificity for each instrument were calculated based on the ability to

identify participants with Claus lifetime risk equal to or above 15%. Sensitivity reflects the proportion of individuals with an elevated lifetime risk of developing breast cancer as identified by the Claus Model who were correctly identified by the screening tool as needing a referral. Specificity reflects the proportion of individuals who did not have an elevated lifetime risk of developing breast cancer by the Claus Model who were correctly identified by the tool as not needing referral.

Positive predictive value and NPV were also calculated for each tool. A PPV represents the likelihood of having an

elevated lifetime risk for breast cancer as identified by the Claus Model when the screening tool also suggests referral is indicated. A NPV indicates the likelihood of not having an elevated lifetime risk for breast cancer as estimated by the Claus Model when the screening tool suggests referral is not needed.

For each screening tool, a receiver operating characteristic curve (ROC curve) was generated with sensitivity along the y axis and (1 minus specificity) along the x axis. The area under the ROC curve (AUC or C-statistic) is an indicator of the accuracy of a screening test. Area under the curve values close to 1.0 represent high levels of both specificity and sensitivity, whereas values near 0.5 or below indicate lack of adequate specificity and sensitivity because no more cases would be identified as needing referral than by chance alone. An AUC of 0.7–0.8 represents good discriminatory accuracy (Amir et al., 2010). The ROC curves and the statistics used for testing differences between ROC curves were estimated through logistic regression using SAS software version 9.4.

Results

Participants were primarily Caucasian and married; all were older than 40 years (Table 3). The Claus calculations

identified 14 of 85 (16%) women whose lifetime risk for breast cancer was $\geq 15\%$. Sensitivity, specificity, PPV, NPV, and AUC for each instrument are presented in Table 4. Sensitivity of the tools ranged from 57.1 to 100, and specificity from 0 to 64.8. Only the Ontario-FHAT and FHS-7 identified all 14 women with elevated risk as needing referral (Table 4). However, the FHS-7 tool flagged all 85 participants as needing referral to a genetic specialist for further analysis and risk assessment.

Area under the curve values for the tools ranged from 0.65 to 0.72 (Figure 1). Chi-square analyses from the logistic regressions were run between each possible pair of tools. All *p* values were $>.05$, indicating that no tool performed significantly differently from another based on AUC. Thus, AUC values were not helpful in discriminating between these tools.

The performance of the Ontario-FHAT was further evaluated by age difference among women who were referred and found to be at elevated risk by the Claus Model (true positives) versus those who were referred and found to not have elevated risk (false positives or overreferrals). Women who were overreferred had a significantly higher average age (55 years old on average) than those who were appropriately referred (47 years old on average), $p = .0098$. This indicates that if the Ontario-FHAT identifies an older woman as needing referral, she is ultimately less likely to be found to have elevated lifetime risk when a full risk assessment calculation is performed (via risk assessment model) when compared with a younger woman.

Discussion

Calculating lifetime breast cancer risk is a complex process, but critical for recommending appropriate screening in cases where family history is suspect. To help with decisions regarding patient referral, the USPSTF issued guidelines in 2014 intended to simplify the task (Moyer, 2014). However, the USPSTF did not give recommendations regarding which tool was superior, stating the evidence was insufficient to make a recommendation (Moyer, 2014). This study may be the first attempt to compare all five recommended screening tools to each other.

This study compared the performance of five USPSTF recommended screening tools to the Claus Model calculations of lifetime breast cancer risk for unaffected women, all of whom had a sister or mother affected by breast cancer. In assessing how each tool performed, of particular interest are 14 of the 85 women whose lifetime risk of developing breast cancer was calculated at $\geq 15\%$ per the Claus Model. In evaluating tool performance, it was important that the tool had the ability to identify all 14 women in the elevated risk category. Only two of the five tools met this standard: the Ontario-FHAT and the FHS-7, thus both had sensitivities of 100%.

Table 3. Demographics

Category	Participants	
	<i>n</i>	%
Age (yr)		
40–49	37	43.5
50–59	29	34.1
60–69	14	16.4
70–74	5	5.9
Race/ethnicity		
Non-Hispanic White	84	98.8
Asian	1	1.2
Education		
High school/GED	13	15.3
Some college/technical school	32	37.6
College graduate and beyond	40	47.1
Marital status		
Married or living as married	68	80.0
Separated or divorced	13	15.3
Widowed	2	2.4
Never married	2	2.4
Total	85	100.0

Table 4. Performance indicators of five screening tools as compared with Claus model

Tool	Sensitivity (%)	Specificity (%)	PPV	NPV	AUC (95% CI)	No. Elevated Risk Women Referred	No. Nonelevated Risk Women Referred
FHAT-Ontario ^a	100	36.62	23.73	100	0.72 (0.61–0.82)	14/14	45/71
Manchester ^b	57.14	64.79	24.24	88.46	0.65 (0.53–0.78)	8/14	25/71
RST ^c	78.57	46.48	22.45	91.67	0.69 (0.55–0.82)	11/14	38/71
PAT ^d	78.57	67.75	26.83	93.18	0.63 (0.50–0.75)	11/14	30/71
FHS-7 ^e	100	0	16.47	0	0.67 (0.57–0.77)	14/14	71/71

Note: AUC = area under the curve; NPV = negative predictive value; PAT = Pedigree Assessment Tool; PPV = positive predictive value; RST = Referral Screening Tool.

^aFamily History Assessment Tool, also called Ontario Family History Assessment Tool (Gilpin et al., 2000).

^bManchester Scoring System (Evans et al., 2004).

^cReferral Screening Tool (Bellcross et al., 2009).

^dFamily History Screen-7 (Ashton-Prolla et al., 2009).

^ePedigree Assessment Tool (Hoskins et al., 2006).

Although the FHS-7 had a sensitivity of 100%, it recommended all 85 women be referred, giving it a specificity of 0%, making it of little clinical utility. Because this tool refers any woman with a single first-degree relative with breast cancer, regardless of the relative’s age at diagnosis, every woman in our study would have been referred to genetics professionals. A 100% referral rate is inefficient and could overload the health care system. Harms of an overloaded health care system may include increased costs and wait times for services. Longer wait times may cause increased anxiety for patients.

In contrast, Ontario-FHAT proved more useful in this sample, identifying all 14 women in the elevated risk

group as needing referral, giving it a sensitivity of 100%. Its NPV was 100%, meaning if it did not identify a patient as needing referral to a genetics professional, it is likely that person did not have an elevated lifetime risk of developing breast cancer (identified as ≥15% lifetime breast cancer risk by the Claus Model).

However, the Ontario-FHAT did not outperform the other tools in all parameters. It had a comparatively low specificity (36.62%). This is not unexpected, as sensitivity and specificity have an inverse relationship in a screening tool (Warner, 2004). The tradeoff between sensitivity and specificity is that to attain high sensitivity (identifying all members of the elevated risk group), the tool can be

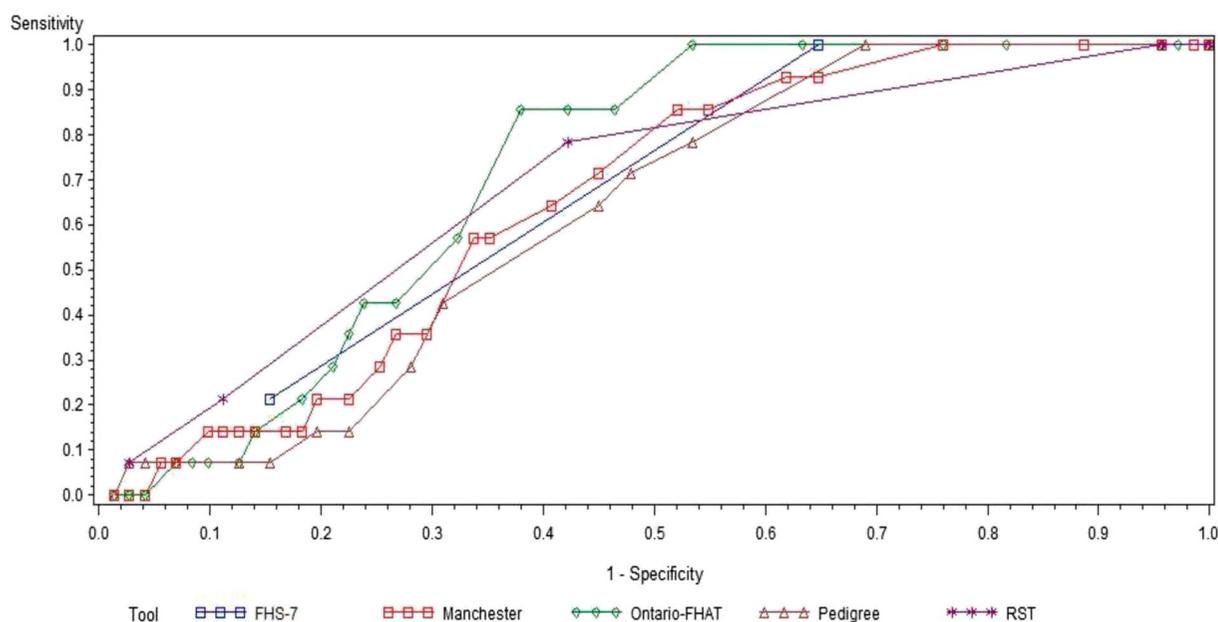


Figure 1. ROC curves for five screening tools to guide referral.

expected to overrefer, decreasing specificity. Conversely, if sensitivity is decreased, meaning some members from the elevated risk group are not identified, specificity can be expected to increase because overreferrals will decrease (Warner, 2004). Thus, because the goal of a screening tool is to identify all women at elevated risk, a higher sensitivity with the resulting lower specificity is desirable. Additionally, if a tool missed women at elevated risk, we miss an opportunity to screen not only the individual but her family members as well, who may also be at additional risk.

The Ontario-FHAT had a low PPV at 23.73, although not the lowest. The PPV reflects the likelihood of a woman having elevated risk if the tool identified her as needing referral (Warner, 2004). For a screening tool, it is reasonable to refer some women at lower risk in preference to missing any women at elevated risk (Warner, 2004), so the low PPV is not undesirable. Additionally, for conditions with low prevalence (in this study, the prevalence of women with elevated risk was 16%), lower PPVs are expected (Warner, 2004). Therefore, a low PPV is not necessarily a negative finding for the Ontario-FHAT.

Overall, the Ontario-FHAT outperformed the other tools. The combination of 100% sensitivity and 100% NPV provides evidence that when the Ontario-FHAT excludes an individual from referral, the individual is unlikely to be at elevated risk.

Limitations

Study limitations include a racially homogenous sample, which may limit application to more diverse populations. In addition, written pedigrees previously collected were used to complete the screening tools rather than using face-to-face interviews. Therefore, at times assumptions about the family history were necessary, which may have altered the data. For example, because we did not have the exact age of menopause for each relative affected with cancer, we counted cancers as occurring before menopause if they occurred at age 50 years or younger because the average age of menopause is 51 years in the United States (National Library of Medicine (US), 2016). These assumptions affected the scoring of the tools and could have varied had we conducted interviews in person.

Additionally, the age and number of participants limit this study. Future researchers should consider including participants as young as age 30 years because screening guidelines (Saslow et al., 2007) for high-risk populations differ beginning at that age and because lifetime risk is higher for younger individuals as they have more lifetime ahead.

Clinical implications

The U.S. Preventive Services Task Force (USPSTF) (2013) recommends that PCPs screen women who have a family

history of breast cancer with one of several screening tools designed to identify a family 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. Based on the findings of this study, the Ontario-FHAT was found to be the best among the tools examined for determining which patients should be referred to genetic specialists. In addition, this tool is easy to use and could be easily implemented into practice.

In addition, as family history is dynamic, primary care clinicians should be prepared to care for the unique and changing attributes of individual patients (American College of Obstetricians and Gynecologists, 2015). Furthermore, assessing breast cancer risk in primary care settings is an ongoing process as a one-time family history assessment may not be sufficient. For example, Zio-gas et al. (2011) found that family histories change significantly between ages 30 and 50 years, necessitating a family history update at least every 5–10 years. The family history update would assure appropriate cancer screening recommendations are done based on changing cancer risk. In addition, if more family members receive cancer diagnoses, an individual's risk estimate may rise. Similarly, an individual's risk level may decrease over time—as age increases, lifetime risk for cancer decreases because there is less time to develop illness.

In addition to changing individual risk, clinicians must also be aware of changes in breast cancer screening guidelines and risk assessment models. For example, recent research suggests it may be better to use 10-year risk estimates rather than lifetime risk scores to determine when breast MRI should be offered as part of an annual screening (Quante et al., 2015).

Additionally, PCPs need to be aware of guidelines for genetic counseling. The USPSTF guidelines (2013) recommend that women with positive screening results should be referred for genetic counseling. Included in the genetic counseling are detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations; education about the possible results of testing and their implications; identification of affected family members who may be preferred candidates for testing; options for screening, risk-reducing medications, or surgery for eligible patients; and follow-up counseling for interpretation of test results (USPSTF, 2013).

In addition, clinicians need to familiarize themselves with new technologies. One such technology is gene panel testing that allows for assessing multiple genes simultaneously for alterations that may contribute to inherited risk for cancers in families rather than sequencing a single gene like *BRCA1* (Hall, Forman, Pilarski, Wiesner, & Giri, 2014).

Furthermore, although the USPSTF screening tools are simpler to use than risk assessment models that calculate lifetime risk (Table 1), clinicians need to be aware of limitations of the tools. None of the screening tools account for age in assigning risk. Therefore, the tools may overestimate the need for referral in older women. Additionally, scoring the tools can be complex. Each tool is scored differently, and each varies in information considered. Clinicians should carefully supervise office staff if collection of data and scoring these tools is delegated, especially as staff learns to use and score the tools.

Clinicians may question if it is not more effective to order genetic tests for all patients with concerning family histories and/or those who are concerned about breast cancer risk. Current research reports that general screening would identify many carriers who are not evaluated by general testing based on family history (Gabai-Kapara et al., 2014; King, Levy-Lahad, & Lahad, 2014). Certainly, the cost of genetic testing has dropped and inexpensive multigene panels are now available. Also, evidence now suggests that population-based *BRCA1* and *BRCA2* testing is the most cost-effective strategy compared with the current policy of family history *BRCA1/BRCA2* testing (Manchanda et al., 2018). However, patients and clinicians must understand that lack of a positive result does not rule out a hereditary basis for the cancer. Similarly, lack of a positive result does not mean risk is low. Only 5–10% of breast cancers are thought to be hereditary (caused by heritable genetic mutations) (National Comprehensive Cancer Network, 2019), and of those, only 10% are caused by *BRCA1/2* mutations, despite the fact that mutations in these genes are the most commonly identified cause of hereditary breast cancer (NCCN, 2019). Indeed, in this study population, all 85 women had a relative with an uninformative negative *BRCA1/2* test, yet 16% were still at elevated risk for developing breast cancer based on family history alone. Thus, although genetic testing can be helpful, it is only part of the equation in caring for women with concerning family histories of breast cancer.

Caring for women at risk for breast cancer is a collaborative process, yet deciding which women to refer may be difficult for clinicians who are not specialists in cancer genetics (Hampel et al., 2015). Primary care providers may choose to refer patients based on results of a brief screening tool, such as those evaluated in this study, or after performing lifetime risk calculation using a risk assessment model described in Table 1. There are advantages and disadvantages to both options. Primary care provider referral of individuals at elevated risk to genetics specialists is recommended by several organizations, including NCCN (2018), the American Cancer Society (Saslow et al., 2007), and USPSTF (Moyer, 2014).

Indeed, the USPSTF rates referring women suspected as being at elevated risk for breast cancer to genetic specialists as a “grade B” recommendation, meaning that it is a preventive service that should be covered by insurance with no cost or co-pay (Moyer, 2014).

An advantage of using the screening tools evaluated in this study is that they take relatively little time to use. In primary care, this may be a significant advantage because limited time has been identified as a barrier to triggering genetic referrals (Hampel et al., 2015). A disadvantage to using these screening tools is that, as demonstrated in this study, they may overrefer or underrefer. Additionally, some of these tools were primarily designed to assess for the likelihood of carrying *BRCA1/2* mutations. They do not screen for other rare cancer syndromes, also potential causes of breast cancer. Finally, none of the USPSTF recommended screening tools to guide referral are intended for the purpose of ordering breast MRI; therefore, none of them has clinical utility beyond referral.

Similarly, there are advantages and disadvantages for PCPs learning how to use risk assessment models. An advantage is that PCPs can order annual screening breast MRI based on lifetime risk calculations using one of the appropriate models (Table 1). However, PCPs who run their own lifetime risk calculations will still find occasion to refer patients. Indeed, the NCCN recommends that if a woman’s risk is calculated to be >20%, she should be referred to a genetics specialist (NCCN, 2018). Although using risk assessment models can be time-intensive, billing codes can be used to cover associated costs (Himes et al., 2016).

Regardless of the route PCPs take to refer women who may be at elevated risk to a genetic specialist, an advantage to referring patients is that genetic specialists have been trained to look for cancer syndromes beyond hereditary breast and ovarian cancer, caused by mutations in *BRCA1/2* genes. Genetic specialists may be more prepared to diagnose rare genetic disease (Hampel et al., 2015).

Finally, USPSTF strongly recommends that when genetic testing is performed, that pretest and posttest counseling with a genetics professional occur, as these professionals are most likely to be able to counsel regarding the legal, personal, and potential financial costs of genetic testing because this is their area of expertise (Moyer, 2014). A similar caution comes from the American College of Medical Genetics and Genomics Practice Guidelines, who write: “...genetic testing...performed without such counseling by qualified clinicians has been associated with...misinterpretation of genetic test results, inappropriate medical management, lack of informed decision making, violation of established ethical standards, adverse psychosocial outcomes, and costly, unnecessary genetic testing,” (Hampel, et al., 2015, p.71).

Conclusion

The purpose of this study was to assess the effectiveness of five tools recommended by the USPSTF to identify women with concerning family histories of breast cancer who were appropriate for referral to genetics professionals for in-depth risk analysis. Although two models identified the 14 participants at elevated risk (i.e., identified by the Claus Model as having a $\geq 15\%$ lifetime breast cancer risk), only the Ontario-FHAT had a combination of sensitivity of 100% and a NPV of 100%. Although the Ontario-FHAT had a lower specificity and PPV, these results are not unexpected in a screening tool where the goal is to identify all participants who are at elevated risk (high sensitivity), although necessarily some who are not at risk will also be referred (lower specificity). The AUC findings were compared and the five tools did not vary significantly from each other. Therefore, of the tools examined, and particularly for clinicians who lack the time or skill to use risk assessment models to calculate lifetime risk of breast cancer, this study suggests the Ontario-FHAT as the best among the tools examined for determining which patients should be referred to genetic specialists.

Authors' contributions: D. O. Himes: contribution to conception and design of work, acquisition of primary and secondary data, data analysis, data interpretation, drafting and revising writing. M. L. Zaro: contribution to conception and design of work, acquisition of secondary data, data analysis, data interpretation, drafting and revising writing. M. Williams: contribution to conception, design of the work, contribution to drafting, revising and critically appraising the work. D. Freeborn: contribution to conception, design of the work, contribution to drafting, revising and critically appraising the work. D. L. Eggett: contribution to conception, design of the work, data analysis, data interpretation, contribution to drafting, revising and critically appraising the work (statistical analysis and results). A. Y. Kinney: contribution to the acquisition and interpretation of data, revising the work and critically appraising for important intellectual content.

Competing interests: The authors report no conflicts of interest.

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The authors and planners have disclosed that they have no financial relationships related to this article.

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