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Title

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Journal

Public Health Genomics, 19(6)

ISSN

1662-4246

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Publication Date

2016

DOI

10.1159/000452095

Peer reviewed

Validation of an Efficient Screening Tool to Identify Low-Income Women at High Risk for Hereditary Breast Cancer

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Keywords

Genetic counseling referral · Hereditary breast cancer · Low income · Screening tool · Validation

Abstract

Background/Aims: We compared the 6-Point Scale, a screening tool to identify low-income women for referral to genetic counseling, with genetic counselors' (GCs') recommendation and the Referral Screening Tool (RST). **Methods:** RST and 6-Point Scale scores were computed for 2 samples: (1) S1, public hospital mammography clinic patients in 2006–2010 ($n = 744$), classified by GCs as high risk (meriting referral to counseling) or not high risk, and (2) S2, primary care patients enrolled in an education intervention study in 2011–2012 ($n = 1,425$). Sensitivity, specificity, and area under the ROC curve (AUROC) were computed for the 6-Point Scale score versus GC and RST classification as high risk. **Results:** The 6-Point Scale had low sensitivity (0.27, 95% confidence interval [CI] 0.21–0.34) but high specificity (0.97, 95% CI 0.95–0.99) and AUROC (0.85, 95% CI 0.81–0.90) versus GC classification, and high sensitivity (S1: 0.90, 95% CI 0.79–1.00; S2: 0.94, 95% CI 0.87–0.97), specificity (S1: 0.95, 95% CI 0.93–0.97; S2: 0.94,

95% CI 0.93–0.96), and AUROC (S1: 0.98, 95% CI 0.96–0.99; S2: 0.98, 95% CI 0.98–0.99) versus the RST. **Conclusion:** The 6-Point Scale compared favorably with the RST, a validated instrument, and is potentially useful as a simple tool for administration in a safety net setting, requiring minimal time investment by primary care physicians and their staff and no financial investment in tablet computers or software.

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Introduction

While hereditary breast cancer is relatively rare, with 5–10% of breast cancers due to BRCA1 and BRCA2 mutations [1], carriers of deleterious mutations in these tumor suppressor genes are at much higher risk for breast and ovarian cancer than the general population. The risk of developing breast cancer by the age of 70 years is 46–71% for women with a harmful BRCA1 or BRCA2 mutation [2]. The risk of developing ovarian cancer by the age of 70 years is 41–46% for BRCA1 mutation carriers and 17–23% for BRCA2 mutation carriers [2]. In contrast, the lifetime risks of being diagnosed with breast cancer or

ovarian cancer are 12 and 1.3%, respectively, in the general US population [3]. Once identified, carriers have several options that have been shown to reduce incidence and/or mortality, including prophylactic surgery, enhanced screening, and chemoprevention [4]. However, it is estimated that >90% of BRCA1/2 mutation carriers have not been identified [5], with the uninsured and people of color disproportionately represented in this undetected population [6–8]. Only 13% of non-Ashkenazi women tested for BRCA1/2 mutations in 2006–2008 were of non-European descent, with African-American and Latina women 4–5 times less likely to receive testing than women of Western European ancestry [9].

Until recent years, the primary means through which women have accessed genetic counseling has been self-referral, typically by those who are well educated and have the means to pay or insurance coverage for the costly test, and there has been considerable variation in insurance coverage for counseling and testing [10]. In addition, primary care clinicians and many mammography clinics may collect family history information, but referrals to genetic counseling have been inconsistent [11]. Access to counseling and testing for the uninsured and those of low income is a recent development. In 2002, foundation-funded risk programs offering free services were established in some public hospitals around the USA [12], after which time Medicaid began to pay for counseling and testing in several states [10]; now the Affordable Care Act considers counseling and testing of high-risk women without a personal history of BRCA-related cancer a covered preventive service [13].

In order to disseminate the benefits of genetic counseling and testing more widely, it is necessary to identify high-risk women in diverse and low-income communities and to provide them with appropriately tailored education and referral to care. Identifying women at risk for hereditary breast cancer involves an assessment of family history, including the number of family members affected with cancer, the types of cancer, and the ages at cancer onset. This can be a lengthy procedure, usually not compensated in primary care. Recent studies have called for an increased focus on efficient assessment tools based on recognized guidelines [14] to help primary care physicians make decisions more easily and reliably regarding when to refer patients for genetic counseling or discuss genetic risks with them [15]. Therefore, it is desirable to have an easy screening tool that can be administered with a minimum of time and effort in a low-resource primary care setting. Toward that end, we developed a strategy to identify high-risk women among the callers to Califor-

nia's statewide telephone service called Every Woman Counts (EWC), which provides access to free breast and cervical cancer screening and assists them in obtaining genetic counseling [16]. Implementing the strategy required a screening tool that could (1) determine quickly and efficiently whether a woman had a family history that warranted genetic counseling and (2) be administered over the telephone by someone who is not trained in genetics. With future use in clinics and community settings in mind, we required a simple, non-tablet-based tool that could be implemented easily as a self-administered scale.

Genetic counseling is recommended in order to determine whether or not a patient's personal and family history warrants genetic testing, and to provide guidance to the patient before and after the test [17]. Several screening tools have been developed to select patients for referral to genetic counseling, including the Pedigree Assessment Tool (PAT), a weighted scoring system that assigns points to family members in both maternal and paternal lineage extending to distant cousins [18], and the Family History Assessment Tool (FHAT) [19]. Both of these are relatively long and complex tools designed for staff administration in clinical settings. For best integration of our risk assessment and referral intervention into the infrastructure of EWC, we modified a simplified version of the PAT that had been developed in our public hospital risk clinic. Features of the modified tool, called the "6-Point Scale," are that it consists of only 10 items, asks about fewer relatives, does not specify lineage, and assesses the most highly weighted indicators first so that the screening process can conclude if the threshold of 6 points, triggering referral to a genetic counselor (GC), is reached (Fig. 1). Details of the development and pretesting of the 6-Point Scale are presented elsewhere [16]. Another simplified tool, the Referral Screening Tool (RST) [20], was validated and published after we had begun using the 6-Point Scale; the 2009 RST defines a positive screening outcome as 2 or more checks on a 19-item checklist that requires a family history of breast and ovarian cancer by lineage.

In order to validate the 6-Point Scale, we compared its selection of high-risk family history profiles for referral to genetic counseling with classification as a positive screen according to the 2009 RST in 2 patient samples. We also compared the 6-Point Scale's selection of family history screeners warranting referral to genetic counseling with GCs' retrospective assessment of the need for referral to formal genetic counseling in 1 of the samples. Here we present our validation of the family history screening tool we designed for brief and easy administration by telephone and for maximum accuracy.

Six Point Scale**Final used in Statewide Study (2/23/10)***(Once the score hits 6, stop and go on to the next step for scores 6 or above.)***1. Have you ever been told by a doctor that you have breast cancer?**

- 1a. No ☐ = 0
1b. Don't know ☐ = 0
1c. If Yes, were you diagnosed before the age of 50? ☐ = 4
Yes ☐ = 2
No ☐ = 2
Don't know ☐ = 2

*If caller says she doesn't know age, prompt her by asking "do you think that it was before or after age 50?"***2. Have you ever been told by a doctor that you have ovarian cancer?**

- 2a. Yes ☐ = 6
2b. No ☐ = 0
2c. Don't know ☐ = 0

3. Do you have any Jewish ancestors?

- 3a. Yes ☐ = 4
3b. No ☐ = 0
3c. Don't know ☐ = 0

4. Have any men in your family had breast cancer?

- 4a. Yes ☐ = 6
4b. No ☐ = 0
4c. Don't know ☐ = 0

5. Have any of your blood relatives had ovarian cancer?

- 5a. Yes ☐ = 4
5b. No ☐ = 0
5c. Don't know ☐ = 0

*Blood relatives include: parents, grandparents, children, aunts & uncles (not by marriage on both mother's and father's sides), cousins.***6. Has your mother had breast cancer?**

- 6a. No ☐ = 0
6b. Don't know ☐ = 0
6c. If Yes, was she diagnosed before the age of 50? ☐ = 4
Yes ☐ = 2
No ☐ = 2
Don't know ☐ = 2

7. Do you have any sisters who have had breast cancer?

- 7a. No ☐ = 0
7b. Don't know ☐ = 0
7c. If Yes, how many sisters were diagnosed with breast cancer? ☐ = 6
3 or more ☐ = 4
2 ☐ = 2
1 ☐ = 2
7d. If 1 or 2 sisters, was she (either sister) diagnosed before the age of 50? ☐ = 2
Yes ☐ = 0
No ☐ = 0
Don't know ☐ = 0

*If caller says she doesn't know age, prompt her by asking "do you think that it was before or after age 50?"***8. Do you have any daughters who have had breast cancer?**

- 8a. No ☐ = 0
8b. Don't know ☐ = 0
8c. If Yes, was she diagnosed before the age of 50? ☐ = 4
Yes ☐ = 2
No ☐ = 2
Don't know ☐ = 2

*If caller says she doesn't know age, prompt her by asking "do you think that it was before or after age 50?"***9. Have either of your grandmothers had breast cancer?**

- 9a. No ☐ = 0
9b. Don't know ☐ = 0
9c. If Yes, was she diagnosed before the age of 50? ☐ = 4
Yes ☐ = 2
No ☐ = 2
Don't know ☐ = 2

*If caller says she doesn't know age, prompt her by asking "do you think that it was before or after age 50?"**If total score is zero after question #9, end call with script for scores of five or lower***10. Have any of your aunts had breast cancer?**

- 10a. No ☐ = 0
10b. Don't know ☐ = 0
10c. If Yes, was she diagnosed before the age of 50? ☐ = 4
Yes ☐ = 2
No ☐ = 2
Don't know ☐ = 2

*If caller says she doesn't know age, prompt her by asking "do you think that it was before or after age 50?"*Final total (pages 1 + 2) = ☐

Fig. 1. The 6-Point Scale items. Originally published in Public Health Genomics 2015;18:65–66, erratum to the article by Joseph et al. [16], reprinted with permission from S. Karger AG, Basel.

Does cancer run in your family?

Your age _____

Ethnicity: ☐ Hispanic/Latino ☐ Native American

PLEASE CHECK ALL ☐ Black/African-American ☐ White/Caucasian

THAT APPLY ☐ Asian/Pacific Islander ☐ Other _____

Are any of your ancestors Jewish? ☐ Unsure ☐ Yes ☐ No

☐ Check the box if you **don't** know about your father's side of the family.

☐ Check the box if you **don't** know about your mother's side of the family.

Patient label

1. Have you or any of your relatives ever been diagnosed with cancer?
If **yes**, please write in the boxes below the **number** of relatives who have had cancer and what type of cancer they had. For example, if you have two sisters who have had breast cancer, write the number 2 in the breast cancer box.

Your family	Breast cancer	Diagnosed before age 50?	Cancer of the ovaries**	Other cancer (please list type)
Yourself				
Sister(s)				
Brother(s)				
Daughter(s)				
Mother				
Father				
Father's mother				
Father's sister(s)				
Mother's mother				
Mother's sister(s)				
Other relative				

Please include only cancer of the **ovaries when you answer this question, not cancer of the uterus or cancer of the cervix.

2. Have any **men** in your family ever been diagnosed with breast cancer? ☐ Yes ☐ No ☐ Unknown

3. May we contact you to discuss your family history of cancer? ☐ Yes ☐ No ☐ Best number to reach you: _____

Fig. 2. Mammography clinic family history screener. Originally published by Lee et al. [12], reprinted with permission from Mary Ann Liebert, Inc.

Subjects and Methods

Patient Samples

We used 2 samples of patients to perform our comparisons. The first sample consisted of public hospital mammography clinic patients (S1). As part of their medical care, all women receiving screening mammography at San Francisco General Hospital (SFGH) are requested to complete a family history screener in their preferred language (English, Spanish, Chinese, or Russian) about their personal and family history of breast, ovarian, and other cancers (Fig. 2). These screeners are read by a GC or genetic counseling assistant, who classifies screeners into 3 groups: (a) family history of cancer highly suggestive of hereditary breast/ovarian cancer predisposition (group A – high risk); (b) family history with some cancer, but not suggestive of breast/ovarian hereditary cancer predisposition (group B – not high risk); and (c) no family history. In order to obtain approximately equal numbers of high-risk and not-high-risk screeners, a stratified sampling scheme was used to select the validation sample from those completed in 2006–2010, including all from group A and a simple, random sample from group B selected using a computer-generated sequence of random numbers.

Our S1 sample size was designed to produce estimates of agreement and sensitivity with satisfactory precision. If $\kappa = 0.70$, a sam-

ple size of 700 screeners, with 50% high risk, produces a 95% confidence interval (CI) of 0.65–0.75. If the sensitivity is 0.90, a sample size of 350 high-risk screeners produces a 95% CI of 0.87–0.93. Because the National Comprehensive Cancer Network (NCCN) guidelines for referral to counseling have changed over time [21, 22], and to ensure that classification criteria were applied consistently, 2 licensed, master's-level GCs independently reviewed the screeners and reclassified them as high risk or not high risk according to current (2011) guidelines; a third GC reviewed and adjudicated screeners with discrepant ratings.

The second sample consisted of primary care patients participating in a randomized controlled trial (S2). Data were included from all participants who completed the baseline interview for the BreastCARE study, which tested a breast cancer risk reduction education intervention among women scheduled for an appointment with their primary care doctor at SFGH or University of California San Francisco (UCSF)'s general medicine practices [23]. The women completed the risk assessment questionnaire by telephone or tablet computer in their preferred language (English, Spanish, or Chinese) before their appointment in 2011–2012. Eligibility for the study included being aged 40–75 years and having no personal history of breast cancer. It is possible that some individuals in S2 were also included in S1.

Table 1. Characteristics of 2 samples: mammography clinic patients, SFGH, 2006–2011, by family history screener risk group ($n = 744$), and primary care patients, BreastCARE study, San Francisco, 2011–2012 ($n = 1,425$)

	SFGH			BreastCARE study baseline ($n = 1,425$)
	confirmed as high risk ($n = 351$)	reclassified as high risk ($n = 59$)	confirmed as not high risk ($n = 334$)	
Age				
<40 years	43 (12)	1 (2)	6 (2)	0 (0)
40–49 years	90 (26)	9 (15)	66 (20)	379 (27)
50–64 years	171 (49)	29 (49)	157 (47)	747 (52)
≥65 years	27 (8)	9 (15)	32 (10)	299 (21)
Unknown	20 (6)	11 (19)	73 (22)	0 (0)
Mean $\pm$ SD, years	51.6 $\pm$ 10.4	56.5 $\pm$ 10.1	54.6 $\pm$ 9.1	56.3 $\pm$ 8.9
Min.–max., years	21–87	38–83	27–84	40–75
Race/ethnicity				
Latina/Hispanic	87 (25)	14 (24)	91 (27)	326 (23)
NH Black	55 (16)	6 (10)	26 (8)	326 (23)
NH Asian/Pacific Islander	90 (26)	23 (39)	142 (43)	273 (19)
NH White	100 (28)	12 (20)	47 (14)	476 (33)
Other/multiracial/unknown	19 (5)	4 (7)	28 (8)	24 (2)
Language ^a				
English	237 (68)	35 (59)	162 (49)	1,146 (80)
Spanish	50 (14)	10 (17)	72 (22)	171 (12)
Russian	9 (3)	4 (7)	6 (2)	0 (0)
Chinese	55 (16)	10 (17)	94 (28)	108 (8)
Personal or family history of cancer				
Breast/ovarian and other(s)	176 (50)	11 (19)	31 (9)	NA
Breast/ovarian only	147 (42)	40 (68)	107 (32)	NA
Any breast/ovarian ^b	323 (92)	51 (86)	138 (41)	547 (39)
Other(s) only	28 (8)	8 (14)	196 (59)	NA

Values are presented as n (%) unless specified otherwise. Risk groups: genetic counselors' classifications of familial risk based on screener were confirmed or reclassified as high risk (warrants genetic counseling) or not high risk (does not warrant genetic counseling). All variables differ significantly across risk groups by χ^2 tests or ANOVA ($p < 0.0001$). SFGH, San Francisco General Hospital; NH, non-Hispanic; NA, not available. ^a SFGH: language of family history screener; BreastCARE study: primary language. ^b SFGH: subtotal of breast/ovarian and other(s) and breast/ovarian only; BreastCARE study: eligibility criteria included having no personal history of breast cancer.

Statistical Analysis

Patient Characteristics (Table 1): In S1, 3 family history screener risk groups were defined based on the review for this study in 2011 as (1) confirmed as high risk, (2) reclassified as high risk, and (3) confirmed as not high risk. In each risk group, frequencies and percentages were computed for demographic characteristics (age group, race/ethnicity, and language of screener) and personal/family history of cancer (breast/ovarian and other[s], breast/ovarian only, other[s] only, or none; any breast/ovarian); descriptive statistics (mean, standard deviation, minimum, and maximum) were computed for age. The age cut-points in Table 1 at 40 and 50 years correspond to age cut-points for mammography recommendations by the US Preventive Services Task Force [24]; at the age of 65 years, most US residents become eligible for Medicare health coverage, which pays for screening mammograms and breast cancer treatment. The risk groups were compared with respect to these

characteristics using χ^2 tests for categorical variables and ANOVA for numeric age. Frequencies and descriptive statistics were also computed for S2.

Distribution of 6-Point Scale and RST Scores (Table 2): The 6-Point Scale was computed for S1 and S2 using all 10 items, so that scores >6 were possible. RST scores were computed for S1; the RST score had been computed previously for S2 [23]. When computing the 6-Point Scale and the RST from S1, we assumed that an entry in the column labeled “diagnosed before age 50?”, which is next to the column labeled “breast cancer” (Fig. 2), referred to age at diagnosis of breast cancer for females whether or not there was an entry in the adjacent “breast cancer” box. Also, because the screener in S1 asked for diagnosis before age 50 and the survey in S2 asked for diagnosis before age 51, it was necessary to compute the 6-Point Scale and the RST using the same age cut-points (50 years in S1, 51 years in S2). Frequencies and percentages for the

Table 2. Six-Point Scale scores and RST scores in 2 samples: mammography clinic patients, SFGH, 2006–2011, by family history screener risk group ($n = 744$), and primary care patients, BreastCARE study, San Francisco, 2011–2012 ($n = 1,425$)

	SFGH			Breast-CARE study baseline ($n = 1,425$)
	confirmed as high risk ($n = 351$)	reclassified as high risk ($n = 59$)	confirmed as not high risk ($n = 334$)	
6-Point Scale score				
0	27 (8)	7 (12)	195 (58)	860 (60)
2	22 (6)	5 (8)	93 (28)	177 (12)
4	120 (34)	38 (64)	35 (10)	199 (14)
≥6	182 (52)	9 (15)	11 (3)	189 (13)
RST score				
0	51 (15)	12 (20)	289 (87)	1,019 (72)
1	178 (51)	43 (73)	42 (13)	281 (20)
≥2	122 (35)	4 (7)	3 (1)	125 (9)
6-Point Scale score × RST score				
<6, <2	160 (46)	50 (85)	322 (96)	1,228 (86)
≥6, <2	69 (20)	5 (8)	9 (3)	72 (5)
<6, ≥2	9 (3)	0 (0)	1 (0)	8 (1)
≥6, ≥2	113 (32)	4 (7)	2 (1)	117 (8)

Values are presented as n (%). Risk groups: genetic counselors' classifications of familial risk based on screener were confirmed or reclassified as high risk (warrants genetic counseling) or not high risk (does not warrant genetic counseling). RST score ≥2: warrants referral to genetic counseling; 6-Point Scale score ≥6: warrants referral to genetic counseling. RST, Referral Screening Tool [20]; SFGH, San Francisco General Hospital.

6-Point Scale and RST, and their cross-classification, were computed for each risk group in S1 and separately in S2.

Comparison of the 6-Point Scale with GC Classification and the RST (Table 3): Agreement between the 6-Point Scale score (≥6 vs. <6) and each of the other methods – final GC risk classification (high vs. not high) in S1, and RST score (≥2 vs. <2) in S1 and S2 – was assessed using the kappa statistic, along with its 95% CI, with the strength of agreement interpreted as recommended by Landis and Koch [25]. Then, with the final GC risk classification and RST score as “gold standards,” the sensitivity, specificity, positive predictive value, and negative predictive value were computed for the 6-Point Scale score, as well as the proportion classified as high risk by each method; in S1, observations were weighted by the inverse probability of selection, and 95% CIs were computed that accounted for the stratified sampling design. Treating the 6-Point Scale as numeric, the area under the ROC curve (AUROC) was computed with respect to each of the other methods using logistic regression; in S1, observations were weighted by the inverse probability of selection, and the bootstrap method [26] was used to compute 95% CIs, as is recommended for the area under a weighted ROC curve [27]. Analyses for S1 were conducted using SAS, version 9.3; analyses for S2 were conducted using Stata, version 11.2.

All study activities were approved by the UCSF Institutional Review Board.

Results

Of the screeners completed in 2006–2010, a total of 352 were initially classified as high risk (group A) and 5,705 as not high risk (group B), with a random sample of 467 selected from group B. After excluding multiple screeners identified with the same medical record number and screeners with no personal or family history of cancer, the validation sample ($n = 744$) consisted of 351 from group A confirmed as high risk, 334 from group B confirmed as not high risk, and 59 from group B reclassified as high risk by GC review. As shown in Table 1, the 3 risk categories differed significantly with respect to demographic characteristics and, as expected, personal or family history of cancer (all $p < 0.0001$). Screeners confirmed as high risk had higher proportions of younger women, non-Hispanic (NH) White and NH Black women, and English-language screeners compared to those reclassified as high risk or confirmed as not high risk. In the group confirmed as high risk, 92% had a personal or family history of breast or ovarian cancer, with half having a history of both breast/ovarian and other cancer(s). In contrast, the group reclassified as high risk primarily consisted of women with a personal or family history of breast/ovarian but no other cancer (68%), and 59% of the group confirmed as not high risk reported a history of other cancer(s) only. S2 overall had more NH Whites and English speakers than S1, and a lower proportion with a personal/family history of breast/ovarian cancer (39%), reflecting the eligibility criterion excluding women with a personal history of breast cancer.

As shown in Table 2, these differences in history are reflected in the distribution of 6-Point Scale scores and RST scores in S1. In the group confirmed as high risk, 52% had 6-Point Scale scores ≥6, compared to 15% in the group reclassified as high risk and 3% in the group confirmed as not high risk; similarly, 35% of the group confirmed as high risk had RST scores ≥2, versus 7% of the group reclassified as high risk and 1% of the group confirmed as not high risk. In S2, 13% had 6-Point Scale scores ≥6, and 9% had RST scores ≥2. The cross-classification of the 6-Point Scale and RST scores shows that most women who had RST scores ≥2 also had 6-Point Scale scores ≥6: 113/122 in the group confirmed as high risk, 4/4 in the group reclassified as high risk, 2/3 in the group confirmed as not high risk, and 117/125 in S2.

As shown in Table 3, the 6-Point Scale classified a greater proportion of women in S2 as high risk (0.13, 95% CI 0.12–0.15) than in S1 (0.08, 95% CI 0.06–0.10), and the GCs classified a much greater proportion of S1

Table 3. Comparison of 6-Point Scale score with GC classification and/or the RST as warranting referral to genetic counseling in 2 samples: mammography clinic patients, SFGH, 2006–2011 ($n = 744$), and primary care patients, BreastCARE study, San Francisco, 2011–2012 ($n = 1,425$)

	SFGH ($n = 744$)		BreastCARE study ($n = 1,425$)
	GC classified as high risk, estimate (95% CI)	RST score positive screen, estimate (95% CI)	RST score positive screen, estimate (95% CI)
Sensitivity	0.27 (0.21, 0.34)	0.90 (0.79, 1.00)	0.94 (0.87, 0.97)
Specificity	0.97 (0.95, 0.99)	0.95 (0.93, 0.97)	0.94 (0.93, 0.96)
Positive predictive value	0.68 (0.55, 0.82)	0.44 (0.31, 0.56)	0.62 (0.55, 0.69)
Negative predictive value	0.83 (0.80, 0.87)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)
κ value	0.41 (0.36, 0.46)	0.64 (0.58, 0.71)	0.72 (0.66, 0.77)
Area under the ROC curve	0.85 (0.81, 0.90)	0.98 (0.96, 0.99)	0.98 (0.98, 0.99)
Proportion at high risk			
GC or RST	0.21 (0.18, 0.24)	0.04 (0.03, 0.05)	0.09 (0.07, 0.10)
6-Point Scale	0.08 (0.06, 0.10)	0.08 (0.06, 0.10)	0.13 (0.12, 0.15)

GC, genetic counselor; RST, Referral Screening Tool [20]; SFGH, San Francisco General Hospital; CI, confidence interval.

women as high risk (0.21, 95% CI 0.18–0.24). Consequently, the sensitivity of the 6-Point Scale with respect to the GC classification was low (0.27, 95% CI 0.21–0.34); however, the specificity was high (0.97, 95% CI 0.95–0.99) and the κ value indicated moderate agreement (0.41, 95% CI 0.36–0.46). In addition, the AUROC was high (0.85, 95% CI 0.81–0.90), suggesting that another cut-point corresponded more closely to the GC classification.

In contrast, the RST classified a smaller proportion of women as high risk (S1: 0.04, 95% CI 0.03–0.05; S2: 0.09, 95% CI 0.07–0.10). The sensitivity of the 6-Point Scale with respect to the RST was high (S1: 0.90, 95% CI 0.79–1.00; S2: 0.94, 95% CI 0.87–0.97), as were the specificity (S1: 0.95, 95% CI 0.93–0.97; S2: 0.94, 95% CI 0.93–0.96) and AUROC (S1: 0.98, 95% CI 0.96–0.99; S2: 0.98, 95% CI 0.98–0.99); the κ value indicated substantial agreement (S1: 0.64, 95% CI 0.58–0.71; S2: 0.72, 95% CI 0.66–0.77).

Discussion

The 6-Point Scale was designed to capture systematically a GC's selection of personal and family history of breast/ovarian cancer screeners for referral to counseling; however, the counselors rated many more history screeners as warranting genetic counseling than did the 6-Point

Scale. The proportion rated as high risk by GCs (21%) was somewhat higher than the proportion rated as high risk (17%) among those with a positive family history of cancer at the same mammography clinic reported in an earlier study [12], perhaps reflecting the change in guidelines. Among screeners confirmed as high risk, only about half (52%) had a 6-Point Scale score meeting the cutoff of 6 points; among those reclassified as high risk, only 15% reached a score of 6. It seems that GCs generally used the same facts as the 6-Point Scale, but they set the bar lower for referral to formal genetic counseling when considering the personal and family history of breast/ovarian cancer, with 86% of those confirmed as high risk and 80% of those reclassified as high risk having a 6-Point Scale score of ≥ 4 . A score of 4 can be obtained by having (1) a diagnosis of breast cancer before the age of 50 years in the patient or 1 relative (mother, sister, daughter, grandmother, or aunt); (2) a diagnosis of breast cancer after the age of 50 years in the patient and 1 relative, in 2 sisters, or in relatives from 2 different categories (e.g., mother and aunt); (3) any blood relative with ovarian cancer; or (4) Jewish ancestors.

On the other hand, a score of ≥ 6 identified most patients classified as high risk by the RST in both S1 (90% sensitivity) and S2 (94% sensitivity). The positive predictive value of the 6-Point Scale with respect to the RST was substantially lower in S1 than in S2; this is mainly due to the lower prevalence of high-risk women estimated from

S1. The RST was somewhat more conservative than the 6-Point Scale in rating women as high risk, with 20% of the GC-confirmed high-risk women classified as high risk by the 6-Point Scale but not by the RST, versus 3% classified as high risk by the RST but not by the 6-Point Scale. The RST gives less weight to breast cancer diagnosed after the age of 50 years than does the 6-Point Scale. For example, histories that are considered high risk by the 6-Point Scale but not by the RST include (1) one relative (e.g., sister) diagnosed with breast cancer before the age of 50 years and another after the age of 50 years, (2) 3 relatives (e.g., sister, grandmother, aunt) diagnosed with breast cancer after the age of 50 years, (3) Jewish ancestry and 1 relative diagnosed with breast cancer after the age of 50 years, and (4) 1 relative with ovarian cancer and 1 relative diagnosed with breast cancer after the age of 50 years. The 6-Point Scale uses summary histories of ovarian cancer in relatives and breast cancer in relatives of the same type (except sisters); histories that are considered high risk by the RST but not by the 6-Point Scale include (1) ovarian cancer in 2 relatives and (2) breast cancer in 2 aunts before the age of 50 years. The comparison of the 6-Point Scale with the RST gave sensitivity and specificity results [20] similar to a comparison of the RST with the FHAT [19], another risk assessment screener designed to identify patients for referral to genetic counseling.

A fair number (15%) of screeners initially classified as not high risk were reclassified as high risk by GC review. The NCCN Guidelines for Genetic/Familial High-Risk Assessment changed over the time that screeners were collected and reviewed by GCs as part of clinical practice. The 2006 NCCN Guidelines [21] included individuals with breast cancer under the age of 50 years, personal and/or family history of male breast cancer, 2 primary breast cancers, and the combination of breast and ovarian cancer in either the same individual or on the same side of the family. Additional “red flags” for cancer risk assessment included combinations of cancers known to be associated with hereditary cancer syndrome, a known mutation in the family, or a history of breast or ovarian cancer in a high-risk population. The 2011 NCCN Guideline [22] criteria were amended to include individuals with triple-negative breast cancer, individuals with breast cancer at any age who had at least 1 close relative with breast cancer at the age of 50 years or younger, or a relative with ovarian or fallopian tube cancer. For individuals without breast cancer, a family history of 2 primary breast cancers at any age on the same side of the family or a family history of ovarian cancer, or the combination of breast and

pancreatic cancer, were sufficient to warrant a risk assessment. These guidelines cast a wider net than either the 6-Point Scale or the RST applied with their designated cut-points.

The demographic differences between the screener risk groups are not unexpected. Women with a family history of breast cancer are likely to undergo mammography screening at a younger age compared to other women [28, 29]. Whites are more likely to report having a family history of cancer than non-Whites [30, 31] and immigrants [32], which may be due in part to the reluctance of families to discuss cancer [33]. Therefore, women at high risk of hereditary breast/ovarian cancer who are unaware of their family history are likely to be classified inaccurately by any screener, unless their personal history of cancer is sufficient to warrant genetic counseling.

Our study has some limitations. First, the mammography clinic history screener was not designed to capture information with calculation of the 6-Point Scale and the RST in mind; therefore, it was necessary to make some assumptions, in particular, to assume that patients understood that the column labeled “diagnosed before age 50?” referred to a diagnosis of breast cancer. In addition, the screener does not have a question about bilateral breast cancer, so it was not possible to compute later versions of the RST [34]. Although the recommendations for referral to genetic counseling have changed over time [21, 22], GCs were able to apply the same standard to all screeners with a final review. In addition, the weighting of data from screeners that were reclassified as high risk resulted in larger 95% CIs for sensitivity than would have been the case with unweighted data. There may have been a selection bias resulting in a high prevalence of family histories of breast/ovarian cancer in S2; nevertheless, the comparison of the 6-Point Scale and the RST produced similar results in both samples.

Our study also has a number of strengths, including fairly large sample sizes, a comparison with review by professional GCs as well as a validated screening tool, and validation in both real-world and research settings.

Conclusion

The 6-Point Scale is potentially useful as a simple tool that can be administered with paper and pencil over the telephone or at primary care clinics in safety net settings by staff not trained in genetics. In a low-resource setting, this tool can be used to prioritize the referral of the high-

est-risk women to genetic counseling easily and reliably, requiring minimal time investment by primary care physicians and their staff and no financial investment in tablet computers or software. It compares favorably with the RST, a validated instrument, in terms of sensitivity and specificity, and the larger proportion of patients classified as high risk compared to the RST is acceptable. Further research is needed to develop a tool suitable for self-administration by patients with low health literacy.

Acknowledgements

This study was funded by grants from Susan G. Komen for the Cure® (SAC110049, R.J. Pasick; KG090504, C.P. Kaplan), the California Breast Cancer Research Program (15OB-0158, C.P. Kaplan), and the National Cancer Institute (R01 CA129096, R.J. Pasick).

Disclosure Statement

The authors declare that they have no conflicts of interest.

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