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Population screening for *BRCA1/BRCA2* founder mutations in Ashkenazi Jews: proactive recruitment compared with self-referral

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Purpose: Population screening of three common *BRCA1/BRCA2* mutations in Ashkenazi Jews (AJ) apparently fulfills screening criteria. We compared streamlined *BRCA* screening via self-referral with proactive recruitment in medical settings.

Methods: Unaffected AJ, age ≥25 years without known familial mutations, were either self-referred or recruiter-enrolled. Before testing, participants received written information and self-reported family history (FH). After testing, both non-carriers with significant FH and carriers received in-person genetic counseling. Psychosocial questionnaires were self-administered 1 week and 6 months after enrollment.

Results: Of 1,771 participants, 58% were recruiter-enrolled and 42% were self-referred. Screening uptake was 67%. Recruited enrollees were older (mean age 54 vs. 48, $P < 0.001$) and had less suggestive FH (23 vs. 33%, $P < 0.001$). Of 32 (1.8%) carriers identified, 40% had no significant FH. Post-test counseling compliance was 100% for carriers and 89% for non-carrier women with FH. All groups expressed high satisfaction (>90%). At 6 months, carriers had significantly increased distress and anxiety, greater knowledge, and similar satisfaction; 90% of participants would recommend general AJ *BRCA* screening.

Conclusion: Streamlined *BRCA* screening results in high uptake, very high satisfaction, and no excess psychosocial harm. Proactive recruitment captured older women less selected for FH. Further research is necessary to target younger women and assess other populations.

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Key Words: Ashkenazi Jewish; *BRCA1*; *BRCA2*; hereditary breast and ovarian cancer; population screening

INTRODUCTION

Identifying unaffected *BRCA1* and *BRCA2* carriers offers prevention and early surveillance opportunities that reduce morbidity and mortality.[1] Although direct-to-consumer testing exists,[2] current medical referrals focus on persons who either are already affected or have significant family history.[3,4] A major limitation of this approach is that approximately half of carriers lack suggestive family history,[5,6] despite being at increased risk for breast and ovarian cancer.[7]

In Ashkenazi Jews (AJ), three common *BRCA1/BRCA2* mutations have a combined carrier frequency of 2.5%.[6,7] Our data[7] suggest that testing for these mutations in AJ fulfills World Health Organization population screening criteria.[8] A recent UK randomized control trial found that testing AJ regardless of family history identified significantly more carriers than family history–based testing without psychological sequelae.[6] However, transitioning from testing limited numbers of high-risk individuals to population-wide screening may require new test delivery strategies. Pretest in-person genetic counseling of many individuals at low a prioi risk may not be feasible or warranted. Previous studies of population screening among AJ in Canada[9] and in Poland[10] used a streamlined approach. Before testing, participants received only written information. After testing, results were provided by telephone to carriers and to non-carriers with significant family history. Carriers were also offered in-person genetic counseling. Participants reported high satisfaction and, in the AJ study, no significant distress.[9–11] However, these studies were performed with self-referred individuals who responded to newspaper notices. A

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formal screening program would proactively recruit participation among eligible individuals. The purpose of this study was to compare streamlined *BRCA* screening via proactive recruitment in medical settings with self-referral.

MATERIALS AND METHODS

The study was approved by the institutional review boards at Shaare Zedek Medical Center, Chaim Sheba Medical Center and Clalit Health Services, and by the Israel National Ethics Committee.

Participants

Participants were AJ (self-defined as four grandparents of AJ origin), age ≥25 years, previously unaffected with cancer, and without a known familial *BRCA* mutation. Participants were not selected based on cancer family history.

Enrollment

Self-referral approximates self-initiated participation in an open-access screening program, whereas recruiter enrollment approximates proactive, medically initiated screening.

Recruiter enrollment

Recruiters offered participation in a mammography center, ambulatory clinics, and an executive screening clinic. Potential participants received written information. People meeting inclusion criteria who declined to participate (refusers) were asked to complete a short sociodemographic survey.

Self-referral

Information about the study was disseminated using posters and brochures provided in hospitals and clinics (including routine breast examination clinics). Interested persons could self-refer by contacting study personnel.

Pretest process

Participants provided written informed consent after receiving written information explaining the study, *BRCA* testing, and testing implications.

Enrollment questionnaire

All participants completed an enrollment questionnaire that requested (i) sociodemographic information, (ii) family history of cancer, and (iii) surveillance habits for breast and ovarian cancer.

Genetic testing

Testing for the AJ founder mutations *BRCA1*-185delAG (c.68_69delAG), *BRCA1*-5382insC (c.5266dupC), and *BRCA2*-6174delT (c.5946delT) was performed as previously published.[7]

Posttesting process

Participants were informed at enrollment that the post-test process would depend on their family history and test results, which were provided within 3 months.

A genetic counselor assessed family-history questionnaires before test results were available. Family history was classified as indicating no, low, moderate, or high likelihood for hereditary breast–ovarian cancer (HBOC) using previously published criteria[7] (**Supplementary Table S1** online). Non-carriers with family history indicating no or low likelihood for HBOC received a letter including test results and routine surveillance recommendations. Non-carriers with moderately or highly suggestive family history and all carriers (regardless of family history) received results by in-person genetic counseling, followed by a summary letter.

Psychosocial assessment

Self-administered questionnaires were sent 1 week after enrollment, before results were received (Q1), 6 months after enrollment, and after results were received (Q2). Questionnaires were e-mailed and Web-based when possible; if not, then they were mailed. They included six psychosocial measures:

1. General satisfaction with participation and testing (5-point scale score: 1–5; very dissatisfied to extremely satisfied).
2. Satisfaction with Health Decision scale (SWHD) (score range: 6–30; low to high satisfaction): SWHD measures satisfaction with health-care decisions,[12] has good psychometric properties, and correlates with "decisional confidence."[13] It has been used to assess HBOC genetic counseling.[14] Each of 6 items has a 5-point scale.
3. State Trait Anxiety Inventory (STAI) (score range: 6–24; low to high anxiety): The 6-item anxiety subscale of the Spielberg State-Trait Anxiety Inventory[15] is a validated, widely used measure of state anxiety. Respondents indicate how they feel "right now, at this moment" using a 4-point frequency scale ranging from "not at all" (1) to "very much so" (4).
4. Impact of Events Scale (IES) (score range: 0–75; no to high distress): The IES is a 15-item self-report measure assessing current subjective distress in relation to a specific stressor,[16] in this case *BRCA* testing. Frequency of intrusive and avoidant ideation and behaviors during the past 7 days is rated using a four-category frequency scale: "not at all" (0), "rarely" (1), "sometimes" (3), and "often" (5). A total score ≥30 indicates significant distress.[16–18]
5. Perceived Personal Control (PPC) (score range: 0–2): The PPC, a validated measure of genetic counseling outcomes, assesses counselees' subjective perceptions of the degree of control they have over their genetic condition.[19] It has high reliability[19,20] and has been used in studies on HBOC predisposition testing.[21–23] The score is the mean of 9 items, each scored 0–2.
6. Knowledge (score range: 0–10): Knowledge of breast cancer genetics and genetic testing was assessed using 10 true–false items (**Supplementary Table S2** online) based on two published knowledge scales[24,25] and modified to apply to individuals at low risk. Modifications were piloted in 20 patients and 10 breast cancer genetics professionals.

Statistical analysis

The mean value of continuous variables was compared using the *t*-test. Frequencies of categorical variables were compared using the chi-square test. Paired *t*-tests and McNemar test were used to compare paired continuous and categorical data, respectively. For multivariate analysis, linear regression and logistic regression were used for continuous and categorical variables, respectively. *P* values are two-tailed with 95% confidence intervals.

RESULTS

Study population

We enrolled 1,771 participants: 1,027 (58%) were recruiter-enrolled and 744 (42%) were self-referred. Sociodemographic characteristics are shown in **Table 1**. Participant mean age was 52 years (SD = 13) and 79% (1,406/1,771) were female. Recruiter enrollees were older than self-referred participants (mean age 54 vs. 48 years, respectively; $P < 0.001$) and were therefore more likely to have ever been married (**Table 1**). A family history consistent with a moderate to high likelihood of HBOC was more common in self-referred than in recruiter-enrolled participants (33 vs. 23%, respectively; $P < 0.001$).

Uptake of *BRCA* testing

Uptake could be evaluated among individuals offered enrollment by a recruiter. Of those, 1,027 (out of 1,530; 67%) consented to participate. Participants and refusers had similar age, gender, and child or daughter status (**Supplementary Table S3** online). Recruitment location significantly affected participation rates, which were 55% in mammography centers, 73% in executive screening clinics, 81% in ambulatory clinics, and 92% when participation was offered by a gynecologist ($P < 0.001$). Recruitment location was the only significant predictor of uptake in multivariate analysis. Compared with ambulatory clinics, recruitment in a mammography center reduced participation by 2.5-fold ($P < 0.001$), whereas recruitment by a gynecologist increased participation by 3.3-fold ($P = 0.005$).

Genetic test results

Genetic testing was completed for all 1,771 participants. Thirty-two (1.8%) mutation carriers were identified: 16 (0.9%) *BRCA1* carriers (185delAG—10 carriers and 5382insC—6 carriers), 15 (0.8%) *BRCA2* 6174delT carriers, and 1 *BRCA1* and *BRCA2* double carrier (185delAG and 6174delT). The carrier rate for females was 26/1,380 (1.8%), which was similar to that for males (6/365; 1.6%). The mean age of female carriers was 45.3 years (SD = 13.6), which was significantly younger than that of non-carriers, whose mean age was 51.4 years (SD = 12.8) ($P = 0.02$) (**Table 2**). The mean age of male carriers was 48.0 years (SD = 16.7) compared with 52.2 (SD = 13.4) years for non-carriers (not significant NS). Carriers were more likely to have a suggestive family history ($P < 0.001$; **Table 2**). Nevertheless, 13/32 carriers (40%) had no or little likelihood of HBOC. The carrier rate was significantly higher in self-referred participants: 21/744 (2.8%) vs. 11/1,027 (1.1%) in recruiter enrollees ($P = 0.006$). However, family history was the only significant predictor of carrier status in multivariate analysis. Compared with participants with no family history, the odds ratios (ORs) for carrier status of participants classified as having low, moderate, or high likelihood for HBOC were 1.2, 3, and 4.5, respectively ($P = 0.02$).

Compliance with post-test genetic counseling for high-risk individuals

All 32 carriers received posttest counseling. Among non-carriers, 468/1,771 (26%) had suggestive family history. Compliance with posttest counseling in this group was 87% (413/468): 93% (245/264) among self-referred vs. 82% (168/204) among recruiter-enrolled participants ($P = 0.002$); compliance was 89% for women vs. 78% for men ($P = 0.01$). Enrollment type was the only significant predictor of counseling compliance in logistic regression, but its absolute effect was negligible (OR = 1.01 for self-referral versus recruiter enrollment; $P = 0.01$). Female gender had borderline significance as a predictor ($P = 0.06$) but had a greater effect (OR = 1.99). Age, education, having children, and family history were not significant predictors of post-test counseling compliance.

Psychosocial assessment

Response to questionnaires. The results described are for 1,255 participants because, due to technical difficulties, the first 516 participants did not receive questionnaires. The response rates were 67% (845/1,255) for Q1 (1 week after testing, before receiving genetic test results) and 50% (623/1,255) for Q2 (6 months after testing, after receiving results). Forty percent (497/1,255) of participants answered both Q1 and Q2, enabling paired analysis in this group.

In univariate analysis, participants who completed Q1 were younger than those who did not complete Q1 (mean age 50.8 vs. 52.0 years; $P = 0.06$). The Q1 response rate was higher for women than for men (51 vs. 36%; $P < 0.001$), among those with a moderate to highly suggestive family history (53 vs. 45% for participants with no to low likelihood of HBOC; $P = 0.004$), and among self-referred participants (56 vs. 43% for recruiter-enrolled participants; $P < 0.001$). In multivariate analysis, the following same factors significantly predicted greater Q1 response: female gender ($P = 0.001$), higher likelihood of HBOC ($P = 0.03$), and type of study enrollment ($P < 0.001$). However, the only substantial OR was for gender (OR = 1.66 for women vs. men). For family history and type of enrollment the OR was approximately 1 (1.055 and 0.999, respectively). Participants' age and education levels did not affect the Q1 response rate. We also called a random sample of 50 nonresponders for Q1. Almost all indicated that they did not respond for technical reasons (e.g., time constraints or incorrect e-mail address).

Psychosocial outcomes. Questionnaire outcomes are summarized in **Tables 3** and **4**. Comparisons of Q2 with Q1 (**Table 3**)

Table 1 Sociodemographic characteristics of study participants: recruiter enrollment versus self-referral

		Recruiter-enrolled	Self-referred	Total	*P* value
Mean age, years (SD, range)		54 (12, 25–88)	48 (13, 25–89)	52 (13, 25–89)	<0.001
		N (%)	*N* (%)	*N* (%)	
Gender	Male	246 (24)	119 (16)	365 (21)	<0.001
	Female	781 (76)	625 (84)	1,406 (79)	
Marital status	Never married	65 (6)	78 (11)	143 (8)	<0.001
	Married	822 (80)	603 (81)	1,425 (81)	
	Divorced or widowed	138 (14)	63 (8)	201 (11)	
Has children	Yes	950 (93)	631 (85)	1,581 (89)	<0.001
	No	77 (7)	113 (15)	190 (11)	
Education	Elementary/high school	87 (9)	49 (7)	136 (8)	NS
	Beyond high school	150 (15)	102 (14)	252 (15)	
	University	756 (76)	578 (79)	1,334 (77)	
Family history: likelihood of HBOC[a]	None to low	719 (70)	451 (61)	1,170 (66)	<0.001
	Moderate to high	231 (23)	246 (33)	477 (27)	
	Insufficient information	77 (7)	47 (6)	124 (7)	
Routine mammogram performance (age ≥50)	Yes	506 (95)	787 (94)	787 (94)	NS
	No	25 (5)	47 (6)	47 (6)	

[a]Likelihood of hereditary breast–ovarian cancer syndrome (HBOC) was based on family-history questionnaires (see Materials and Methods and **Supplementary Table S1** online).

Table 2 Sociodemographic characteristics of carriers versus non-carriers

		Carriers	Non-carriers	*P* value
Mean age, years (SD, range)		46 (14, 27–75)	52 (13, 25–89)	0.013
		***N* (%)**	***N* (%)**	
Gender	Male	6 (19)	359 (21)	NS
	Female	26 (81)	1,380 (79)	
Age (years)	25–39	15 (47)	340 (20)	0.001
	40–59	10 (31)	879 (50)	
	≥60	7 (22)	520 (30)	
Enrollment method	Recruiter	11 (34)	1,016 (58)	0.006
	Self-referral	21 (66)	723 (42)	
Family history: likelihood of HBOC[a]	None to low	13 (41)	1,157 (67)	<0.001
	Moderate to high	19 (59)	459 (26)	
	Insufficient information	–	123 (7)	

[a]Likelihood of hereditary breast–ovarian cancer syndromes (HBOC) was assessed using family-history questionnaires (see Materials and Methods and **Supplementary Table S1** online).[7]

include only non-carriers because Q1 preceded knowledge of genetic status. Q2 outcomes for carriers are described separately (**Table 5**).

Satisfaction with study participation:

In Q1, 91% reported being satisfied or very satisfied with study participation (**Table 3**). Logistic regression indicated that greater perceived control (PPC score) predicted high satisfaction (OR = 7.6; $P < 0.001$), as did self-referral (OR = 2.5; $P = 0.009$). Among recruiter enrollees, in Q1 the recruitment site significantly affected satisfaction rates, which were 80% for gynecologist offices, 84% for executive screening clinics, 91% for mammography centers, and 93% for ambulatory clinics ($P = 0.02$, controlled for PPC). In the entire group, participant age, gender, having children, education level, family history, IES, and knowledge scores did not significantly predict satisfaction. In Q2, total satisfaction increased to 93% (satisfied/very satisfied) and remained higher among self-referred (96%) versus recruiter-enrolled participants (90%) ($P = 0.02$). Satisfaction increased over time. In Q2, more participants were very satisfied than at in Q1 (57 vs. 47%; $P = 0.06$ for paired analysis).

All other psychosocial outcomes were assessed using linear regression; each measure was a dependent variable and the independent variables were the sociodemographic characteristics and other measures (**Table 4**). Satisfaction with participation had significant covariance with SWHD; therefore, only SWHD was included as a satisfaction measure in these analyses.

SWHD

Total mean SWHD score in Q1 was high (25.8/30; SD = 3.3) (**Table 3**). Younger age, self-referral, higher PPC score, and lower IES and STAI-6 scores significantly predicted higher SWHD score, but these factors had only small absolute effects (e.g., self-referral increased SWHD score by 0.6 points; $P = 0.003$; **Table 4**). In Q2, SWHD score remained higher in the self-referred group ($P = 0.012$), but the difference decreased from 1.1 to 0.6 (of 30) points (**Table 3**). In paired analysis, SWHD was higher in Q2 than Q1 ($P = 0.004$).

PPC (range 0–2)

In Q1, mean PPC score was 1.05 (SD = 0.5), which was 0.1 (out of 2) points higher in self-referred versus recruiter-enrolled participants ($P < 0.001$; **Table 3**). Higher SWHD scores, better knowledge, and lower anxiety (STAI-6) were significant but

Table 3 Psychosocial outcomes of *BRCA1/BRCA2* screening: effect of time and enrollment method

		One week after testing (Q1)				Six months after testing (Q2, non-carriers)			
		Enrollment method				Enrollment method			
Psychosocial measure	Outcome	Recruiter	Self-referral	Total	*P*[a]	Recruiter	Self-referral	Total	*P*[a]
Satisfaction[b]	Not/Somewhat satisfied, *N* (%)	54 (12)	20 (5)	74 (9)	<0.001	30 (10)	11 (4)	41 (7)	0.02
	Satisfied, *N* (%)	210 (48)	161 (40)	371 (44)		115 (37)	103 (35)	218 (36)	
	Very satisfied, *N* (%)	175 (40)	225 (55)	400 (47)		166 (53)	179 (61)	345 (57)	
SWHD (6-30)	Mean score (SD)	25.2 (3.2)	26.3 (3.2)	25.8 (3.3)	<0.001	26.2 (3.3)	26.8 (3.1)	26.5 (3.2)	0.01
PPC (0-2)	Mean score (SD)	1.00 (0.5)	1.10 (0.5)	1.05 (0.5)	<0.001	1.18 (0.5)	1.28 (0.5)	1.23 (0.5)	0.006
IES (0-75)	Mean score (SD)	5.4 (7)	6.2 (8.2)	5.8 (7.6)	0.02	4.8 (7.5)	5.6 (7.8)	5.2 (7.7)	NS
STAI-6 (0-24)	Mean score (SD)	9.8 (3.6)	10.2 (3.4)	10.0 (3.5)	NS	9.8 (3.6)	10.2 (3.7)	9.9 (3.6)	NS
Knowledge (0-10)	Mean score (SD)	6.8 (2.6)	7.4 (2.3)	7.0 (2.5)	<0.001	6.8 (2.5)	7.5 (2.2)	7.1 (2.4)	<0.001
Recommend *BRCA* screening[c]	Yes, *N* (%)	348 (87)	329 (85)	677 (86)	NS	266 (91)	244 (89)	510 (90)	NS
	No, *N* (%)	3 (1)	4 (1)	7 (1)		1 (<1)	2 (<1)	3 (<1)	
	Not sure, *N* (%)	51 (13)	55 (14)	106 (13)		24 (8)	28 (10)	52 (9)	

[a]*P* value for comparison of recruiter-enrolled versus self-referred participants. [b]Satisfaction with the entire process (participation and testing). [c]Results shown are for those who answered this question; 39 (6.5%) did not provide an answer.

Table 4 Psychosocial measure scores: effect size of demographic variables, enrollment method, and one unit change in other measures

	Psychosocial measures (dependent variables)											
	Satisfaction		SWHD		PPC		IES		STAI		Knowledge	
	Exp(B)		B		B		B		B		B	
	P value		*P* value		*P* value		*P* value		*P* value		*P* value	
Independent variables[a]	Q1	Q2	Q1	Q2	Q1	Q2	Q1	Q2	Q1	Q2	Q1	Q2
Gender	–[b]	–	–	**0.8** *0.02*	–	–	**3.2** *<0.001*	**3** *0.001*	–	–	**0.5** *0.05*	–
Mean age (years)	–	–	**–0.03** *0.003*	–	–	–	**–0.08** *0.001*	**–0.09** *0.001*	**–0.45** *<0.001*	**–0.03** *0.03*	**–0.03** *<0.001*	**–0.03** *<0.001*
Education	–	–	–	–	–	–	–	**–2.4** *0.003*	–	–	**0.05** *0.014*	**0.9** *0.001*
Likelihood of HBOC	–	–	–	–	–	–	**0.07** *0.009*	–	–	–	–	–
Enrollment method	**2.5** *0.009*	**2.8** *0.02*	**0.6** *0.003*	–	–	–	–	–	–	–	–	–
SWHD	NA	NA	NA	NA	**0.08** *<0.001*	**0.08** *<0.001*	**–0.2** *0.05*	**–0.3** *0.04*	**–0.1** *0.03*	–	–	–
PPC	**7.6** *<0.001*	**2.9** *0.01*	**3.2** *<0.001*	**3.7** *<0.001*	NA	NA	–	–	**–0.85** *0.005*	**–1.2** *0.001*	**1.1** *<0.001*	**0.8** *0.001*
IES	–	–	**–0.03** *0.05*	**–0.03** *0.04*	–	–	NA	NA	**0.1** *<0.001*	**0.09** *<0.001*	–	**0.04** *0.003*
STAI	–	–	**–0.07** *0.03*	–	**–0.01** *0.005*	**–0.02** *0.001*	**0.5** *<0.001*	**0.4** *<0.001*	NA	NA	–	–
Knowledge	–	–	–	–	**0.03** *<0.001*	**0.03** *0.001*	–	**0.4** *0.003*	–	–	NA	NA

HBOC, hereditary breast–ovarian cancer; IES, IES, Impact of Events Scale; NA, not applicable; NS, not significant; PPC, Perceived Personal Control scale; STAI, State Trait Anxiety Inventory; SWHD, Satisfaction with Health Decision scale.

[a]B values (boldface) shown are (i) the change (in points) in each score for gender (females versus males), education (university versus nonuniversity), likelihood of HBOC (high/moderate versus low/none), enrollment method (self-referral versus recruiter enrolled); (ii) for age, the change (in points) in score for each year of older age; and (iii) for psychosocial measures, the change (in points) in the dependent score for each additional point in the independent score. *P* values are indicated in italics. [b] - indicates not signfiicant.

weak, predictors of the PPC score. For example, each 1-point increase in knowledge or SWHD scores increased PPC by only 0.03 points ($P < 0.001$) and 0.08 points ($P < 0.001$), respectively. Other variables did not affect PPC (**Table 4**). Mean PPC score increased to 1.23 in Q2, and the 0.1-point difference between the two enrollment groups was conserved (**Table 3**; $P = 0.006$). For participants who completed both questionnaires, PPC score was significantly higher in Q2 ($P < 0.001$), and the 0.2-point

Table 5 Psychosocial outcomes for carriers versus non-carriers 6 months after testing (Q2)

		Carriers *N* = 19	Non-carriers *N* = 604	*P*
Satisfaction[a]	Not/somewhat satisfied, *N* (%)	2 (10)	41 (7)	NS
	Satisfied, *N* (%)	5 (26)	218 (36)	
	Very satisfied, *N* (%)	12 (63)	345 (57)	
SWHD (6–30)	Mean score (SD)	25.3 (5.3)	26.5 (3.2)	NS
PPC (0–2)	Mean score (SD)	1.43 (0.38)	1.23 (0.49)	NS
IES (0–75)	Mean score (SD)	19.9 (15.6)	4.9 (7.3)	**<0.001**
STAI-6 (0–24)	Mean score (SD)	12.6 (4.2)	9.9 (3.6)	**0.016**
Knowledge (0–10)	Mean score (SD)	8.7 (1)	7.1 (2.4)	**<0.001**
Recommend *BRCA* screening	Yes, *N* (%)	14 (78)	510 (84)	NS
	No, *N* (%)	0	3 (<1)	
	Not sure, *N* (%)	4 (22)	52 (9)	
	Missing, *N* (%)	1(<<1)	39 (6)	

[a]Satisfaction with the entire process (participation and testing).

increase observed was within the range of observed effects of in-person genetic counseling (0.07–0.37).[21,26]

IES (0–75)

The mean IES score in Q1 was 5.8 (SD = 7.6), which was 0.8 (out of 75) points higher among self-referred participants (P = 0.02). IES of more than 30 (indicating high post-event distress) was reported by only 14 (1.7%) individuals: 11/398 (2.7%) self-enrolled and 3/417 (0.7%) recruiter-enrolled (P = 0.02; **Table 3**). In multivariate analysis, female gender, younger age, positive family history, lower SWHD scores, and higher STAI-6 scores were significant predictors of higher IES scores. IES score was 3.2 points higher for women versus men (P < 0.001). Other predictors were weaker; for example, IES score was higher by 0.07 points for participants with moderate to high HBOC likelihood versus those with no to low likelihood (P = 0.009; **Table 4**). In Q2, distress scores decreased slightly, nonsignificantly, to a mean of 5.2 (SD = 7.7) (**Table 3**). Likewise, only 6/587 (1%) participants reported IES >30. No significant difference was found between enrollment groups. Paired analysis showed no significant change in IES scores over time.

STAI

Mean STAI-6 score in Q1 was 10/24 (SD = 3.5). Similar to the IES score, STAI-6 score was higher, although not significantly, among self-referred compared with recruiter-enrolled participants (**Table 3**). Younger age, lower SWHD and PPC scores, and higher IES score were significantly associated with increased state anxiety but had weak absolute effects (e.g., a 0.1 point (of 24 points) increase in STAI-6 score was observed for every additional 1 point (of 75 points) in the IES; P < 0.001; **Table 4**). Paired analysis showed no significant change in anxiety over time.

Knowledge

Mean knowledge score in Q1 was 7.0/10 (SD = 2.5), which was higher for self-referred versus recruiter-enrolled participants (P < 0.001; **Table 3**). Female gender and university education increased knowledge scores very modestly (by 0.5 (P = 0.046) and 0.05 points (P = 0.01), respectively; **Table 4**).

In Q2, the mean knowledge score was slightly higher (7.1; SD = 2.4; NS versus Q1) and remained higher among self-referred versus recruiter-enrolled participants (7.5 (SD = 2.2) and 6.8 (SD = 2.5) respectively; P < 0.001). Paired analysis also showed no significant change in knowledge over time among non-carriers. For non-carriers with a suggestive family history who were invited for post-test genetic counseling, mean knowledge in Q2 was 7.6/10, which was significantly higher (P = 0.002) than for non-carriers without a family history.

Correlation between psychosocial measures

Distress scores (IES) were correlated with anxiety scores (STAI-6) (r_p = 0.3; P < 0.001). PPC scores correlated with SWHD scores (r_p = 0.56; P < 0.001) and with knowledge scores (r_p = 0.25; P < 0.0001); they were inversely correlated with stress level (IES) (r_p = −0.83, P = 0.02). Knowledge was also correlated with the SWHD score (r_p = 0.2; P < 0.001).

Recommendation for *BRCA* screening

Participants were asked whether they would recommend *BRCA* population screening using the same process they experienced. In Q1, 677 (86%) indicated they would recommend screening, 7 (1%) were opposed, and 106 (13%) were unsure (**Table 3**). Of those unsure, some mentioned, in an open remark, that they would support *BRCA* screening if they were assured that testing would be voluntary. The proportion of participants recommending screening was not affected by type of enrollment and increased with time, to 90% at in Q2.

Psychosocial outcomes in carriers versus non-carriers

Psychosocial outcomes in carriers were compared with those of non-carriers after participants received test results (Q2; **Table 5**). Satisfaction level, SWHD, PPC, and recommendation rate for population *BRCA* screening were similar. Significant differences were found for the distress and anxiety measures: mean IES score was 19.9 for carriers versus 4.9 for non-carriers (P < 0.001) and mean STAI-6 score was 12.6 for carriers versus 9.9 for non-carriers (P = 0.02). Knowledge scores were also significantly higher for carriers (8.7 vs. 7.1 for non-carriers; P < 0.001). Paired analysis in carriers showed increased knowledge over time (from 7.5 in Q1 to 8.8 in Q2; not significantly different in this small sample).

DISCUSSION

This trial of population screening for common *BRCA1* and *BRCA2* mutations in unaffected AJ compares possible real-life strategies: recruitment by medical personnel (58%) or self-referral (42%). With a view toward large-scale screening,[9,10] we used a streamlined process of pretest written information. After

testing, in-person genetic counseling was provided for carriers and for non-carriers with a significant family history. Overall, more than 90% of participants reported high or very high satisfaction both 1 week and 6 months after testing, with significantly increased satisfaction over time. The majority would recommend population screening: 86% at 1 week and 90% at 6 months after testing. Only 1% were opposed and the remaining 10–13% were mainly concerned about screening remaining voluntary. Participation rate, measured among recruiter enrollees, was 67%, which was similar to the 71% rate in a recent UK study of AJ.[6] Having children, specifically daughters, did not affect participation, suggesting personal risk assessment was the main motivation for testing. Compliance with post-test counseling was 100% for carriers and 89% for female non-carriers, showing that streamlining did not result in lack of follow-up, regardless of type of enrollment (OR = 1.01).

Compared with self-referral, recruiter enrollment in medical settings captured women less selected for family history. Among recruiter enrollees, 24% indicated a suggestive family history versus 35% of self-referred participants. However, both these rates are substantially higher than the ~10% background rate of breast/ovarian family history among AJ in Israel.[7] Consistent with previous reports,[7,9,10] 40% of carriers identified in this study had no significant family history. Therefore, although family history is a significant motivator for screening, our results reiterate the importance of reaching women without such history. Proactive population-wide recruitment is a step in this direction, but it requires further refinement.

The mean ages of recruiter enrollees and self-referred participants were 54 and 48 years, respectively, which were similar to the mean ages of 54 and 49 years, respectively, observed in studies of AJ in the United Kingdom[6] and Canada.[9] In a self-referral study in Poland,[10] the mean age of female carriers was 45.6 years, which is comparable to 45.3 years in this study. This is substantially older than optimal for cancer prevention in carriers because cancer risks increase sharply with age. Although risks are very low before age 30, by age 50, combined risks for breast cancer and ovarian cancer are 41 and 16% for *BRCA1* and *BRCA2* carriers, respectively.[7] In this and in previous studies of unaffected AJ,[9] the carrier rate was lower than the expected 2.5%, probably because many carriers have already become affected by their late 40s and early 50s. To maximize cancer prevention through *BRCA* screening, it is imperative to develop and empirically validate strategies that engage younger women. This may require identifying concerns specific to this age group, as well as tailoring outreach approaches (e.g., utilizing social media). Empiric assessment is crucial. We originally expected higher uptake in women undergoing routine mammography, presuming this indicates an interest in preventive breast health. Although uptake at a mammography center was appreciable (55%), it was significantly lower than at other locales, perhaps because mammography-associated anxiety reduced receptiveness for additional testing.[27] Conversely, recruitment in clinics and, particularly, recommendation by a physician significantly increased uptake (to >80%).

Recruitment site also affected satisfaction, ranging from 80% for gynecologist referral to 93% for ambulatory clinics. These results indicate the need to optimize recruitment schemes and sites to improve participation and satisfaction. Increasing access is clearly necessary. Despite a significant family history in 29% of participants, none were previously counseled or tested. This could be related to lack of awareness, limited familial communication, and bureaucratic (referral and payment) barriers that a screening program can overcome. Themes regarding access and familial communication, which emerged in extensive qualitative interviews, are reported elsewhere.[28]

Self-referred participants reported greater satisfaction with testing than recruiter enrollees, with higher SHWD scores and better sense of control (PPC), perhaps because their participation was self-initiated. However, their distress (IES) scores were also higher, consistent with the greater a priori risk of self-referred participants, who were younger and more likely to have a suggestive family history. At 6 months after testing, carriers and non-carriers showed similar satisfaction, SWHD, and PPC. Carriers had significantly increased distress and anxiety but also significantly greater knowledge. Compared with previous studies addressing psychosocial outcomes of HBOC genetic counseling and testing, we reported high SWHD scores (>25/30) for all groups (non-carriers, carriers; recruiter-enrolled, self-referred), similar to SWHD scores reported following traditional genetic counseling for *BRCA* testing.[14] Distress (IES) was low (<6) at both time points for both self-referred and recruited non-carriers. In the Canadian AJ self-referral study, mean IES scores were 10.4 at baseline and 10.7 at 1 year. Studies of traditional *BRCA* counseling and testing in general reported higher distress levels,[29,30] but most included women who were affected or at higher a priori risk, whereas in this study all participants were unaffected and 71% had no suggestive family history. Indeed, a suggestive family history, younger age, and lower satisfaction scores predicted higher distress, even though their effect size was small. Knowledge and education did not affect distress levels.

Although in non-carriers distress and anxiety were low and stable over time, among carriers, mean IES and STAI-6 scores at 6 months increased significantly to 19.9 (SD = 15.6) and 12.6 (SD = 4.2). Increased distress and anxiety have been consistently observed at 6 months to 1 year after disclosure of carrier status in studies of traditional, in-person genetic counseling.[31–33] This distress declines over time[34–36] and will be reassessed in future evaluations of study participants. Over time, carriers also undergo risk reduction surgeries that further reduce distress and anxiety.[11,37] In the Canadian AJ study, mean IES score for carriers at 1 year was 23.8 (SD = 14.5) and decreased to 17.2 (SD = 14.5) at 2 years. Importantly, satisfaction with testing (SWHD) was as high in carriers as in non-carriers and, similar to all previous studies, distress and anxiety scores for carriers were generally below the threshold of clinically meaningful psychological dysfunction.[38]

The mean knowledge score 1 week after testing was 7.0/10 (SD = 2.5), similar to knowledge scores of ~70% in previous

studies of education sessions or written information.[39,40] Among women invited for posttest counseling, knowledge increased to 7.6/10 ($P = 0.002$); among carriers, knowledge at 6 months was increased substantially to 8.7/10. In qualitative interviews reported elsewhere,[28] participants indicated that they regarded knowledge on a "need to know" basis, i.e., they sought knowledge only once they were found to be at risk. In this study, 69% of participants were at low a priori risk and remained so after testing. To summarize, psychosocial outcomes were generally favorable and similar to those observed both with traditional genetic counseling and in other non-family-history-based trials.

Study limitations

This study population is highly educated. Recruitment at mammography, executive screening, and breast surgeon clinics ascertained highly health-aware individuals. We did not aim to enroll a representative sample of the Israeli AJ population, but rather to explore alternative options of performing general *BRCA1/BRCA2* screening. In this respect, the study population provides insight into the profile of potential participants in different versions of a screening program. The response rate to questionnaires was partial (67% for Q1 and 50% for Q2), but responders were representative of women study participants. The study was performed in one country. Sociocultural and health-system particulars may differ elsewhere.

Conclusion

Screening AJ for common *BRCA1* and *BRCA2* mutations using a streamlined process without in-person pretest counseling resulted in high (67%) uptake, very high (>90%) satisfaction, and very high post-test counseling compliance (89–100%). Most participants (71%) had no suggestive family history, and restricting in-person counseling to high-risk persons at the post-test stage resulted in no substantial psychosocial harm. Forty percent of carriers identified did not have a suggestive family history. Self-referral and medical-based recruitment captured different groups of women, suggesting that a multimethod approach will widen ascertainment. Current strategies target women who are around age 50, which is older than optimal for effective prevention. Further research is necessary to address screening implementation for younger women and for various societies and health systems.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

The authors declare no conflict of interest.

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