VOLUME 34 · NUMBER 24 · AUGUST 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Noninferiority Trial of Telephone Delivery of *BRCA1/2* Genetic Counseling Compared With In-Person Counseling: 1-Year Follow-Up

Anita Y. Kinney, Laurie E. Steffen, Barbara H. Brumbach, Wendy Kohlmann, Ruofei Du, Ji-Hyun Lee, Amanda Gammon, Karin Butler, Saundra S. Buys, Antoinette M. Stroup, Rebecca A. Campo, Kristina G. Flores, Jeanne S. Mandelblatt, and Marc D. Schwartz

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on June 20, 2016.

Supported by grants from the National Cancer Institute at the National Institutes of Health (1R01CA129142; A.Y.K.) and the Huntsman Cancer Foundation. Also supported by the Shared Resources (P30 CA042014; M.C.B.) at Huntsman Cancer Institute (Biostatistics and Research Design, Genetic Counseling, Research Informatics, and the Utah Population Database) and the University of New Mexico Comprehensive Cancer Center Support Grant: Development Funds and the Biostatistics Shared Resource (P30CA118100; C.L.W.); the Utah Cancer Registry, which is funded by Contract No. HHSN261201000026C from the National Cancer Institute's SEER Program, with additional support from the Utah State Department of Health and the University of Utah; the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant No. 8UL1TR000105 (formerly UL1RR025764). This content is solely the responsibility of the authors and does not necessarily reflect the opinions or views of the funding and supporting agencies.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01346761.

Corresponding author: Anita Y. Kinney, PhD, RN, Cancer Research Facility, 1 University of New Mexico, MSC07-4025, 2325 Camino de Salud NE, Albuquerque, NM 87131-0001; e-mail: aykinney@salud.unm.edu.

0732-183X/16/3424w-2914w/$20.00

DOI: 10.1200/JCO.2015.65.9557

ABSTRACT

Purpose

The ongoing integration of cancer genomic testing into routine clinical care has led to increased demand for cancer genetic services. To meet this demand, there is an urgent need to enhance the accessibility and reach of such services, while ensuring comparable care delivery outcomes. This randomized trial compared 1-year outcomes for telephone genetic counseling with in-person counseling among women at risk of hereditary breast and/or ovarian cancer living in geographically diverse areas.

Patients and Methods

Using population-based sampling, women at increased risk of hereditary breast and/or ovarian cancer were randomly assigned to in-person (n = 495) or telephone genetic counseling (n = 493). One-sided 97.5% CIs were used to estimate the noninferiority effects of telephone counseling on 1-year psychosocial, decision-making, and quality-of-life outcomes. Differences in test-uptake proportions for determining equivalency of a 10% prespecified margin were evaluated by 95% CIs.

Results

At the 1-year follow-up, telephone counseling was noninferior to in-person counseling for all psychosocial and informed decision-making outcomes: anxiety (difference [d], 0.08; upper bound 97.5% CI, 0.45), cancer-specific distress (d, 0.66; upper bound 97.5% CI, 2.28), perceived personal control (d, −0.01; lower bound 97.5% CI, −0.06), and decisional conflict (d, −0.12; upper bound 97.5% CI, 2.03). Test uptake was lower for telephone counseling (27.9%) than in-person counseling (37.3%), with the difference of 9.4% (95% CI, 2.2% to 16.8%). Uptake was appreciably higher for rural compared with urban dwellers in both counseling arms.

Conclusion

Although telephone counseling led to lower testing uptake, our findings suggest that telephone counseling can be effectively used to increase reach and access without long-term adverse psychosocial consequences. Further work is needed to determine long-term adherence to risk management guidelines and effective strategies to boost utilization of primary and secondary preventive strategies.

J Clin Oncol 34:2914-2924. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Increased awareness of associations between *BRCA1/2* mutations and breast and ovarian cancer[1-10] has led to an increased demand for genetic counseling and testing.[11,12] If population-wide *BRCA1/2* screening is realized,[13] the need for evidence-based and efficient counseling care delivery models will also increase. Specialized expertise is required to assess a woman's risk of hereditary breast and ovarian cancer (HBOC), support informed decision-making, provide risk-appropriate care recommendations, and attend to the potential deleterious psychosocial effects of providing new risk information.[14] Providers often lack this specialized knowledge[15,16] leading to suboptimal patient informed decision-making and avoidable distress.[17,18] Increasing access to trained genetic counselors is therefore essential.[19]

Telephone counseling can extend the reach of trained genetic counselors and overcome

geographic access barriers[16,20-26] while reducing costs.[27,28] Concerns remain, however, about whether telephone counseling can support informed decision-making and minimize adverse psychologic outcomes.[12,29-31] Recent evidence indicates that in the short term, telephone counseling is noninferior to in-person counseling for key decision-making and psychosocial outcomes.[27,32] There are no data on longer-term noninferiority for these outcomes after telephone counseling.[33-39]

To fill this gap, we examined 1-year outcomes from a previously reported randomized trial[32] comparing telephone with in-person counseling in a population with potential geographic barriers to care. We hypothesized that telephone counseling would be noninferior to in-person counseling at the 1-year follow-up for psychologic, informed decision-making, quality-of-life, and risk management outcomes. We also assessed geographic differences in follow-up outcomes and described risk management behaviors.

PATIENTS AND METHODS

Research Design and Study Population

A two-armed, parallel-cluster, randomized equivalency/noninferiority trial compared telephone with in-person counseling for deleterious *BRCA1/2* mutations (NCT01346761). Enrollment began August 2010 and ended September 2012. One-year outcome assessments were completed February 2014. Study details and short-term outcomes have been previously published.[32]

The Utah Population Database[40] and Utah Cancer Registry were used to identify and recruit breast and ovarian cancer survivors. At-risk female relatives were recruited through survivors who tested positive for a *BRCA1/2* mutation. Eligible participants were English speaking, 25 to 74 years of age, Utah residents, had personal/family histories meeting HBOC genetic testing guidelines,[41] had telephone access, could travel to in-person counseling at one of 14 clinics, and had no prior genetic counseling and/or *BRCA1/2* testing. The University of Utah and University of New Mexico Institutional Review Boards approved study protocol. All participants provided informed consent.

Randomization and Masking

Participants completed baseline assessments and were randomized by family unit to one of the two study arms using a computer-generated allocation algorithm based on a permuted block randomization plan.[32] Study staff who conducted baseline assessments were blinded to the identity of a woman's participating relative(s).

Interventions

In-person counseling. Women assigned to in-person counseling received counseling by a cancer genetic counselor according to a standardized protocol consistent with national guidelines[32,42,43] and were given an HBOC educational brochure and a copy of the visual aids used during the counseling. Women who decided to have genetic testing could provide a sample at their appointment or bring a *BRCA1/2* buccal test kit home should they decide to test at a later time. Women who chose testing were offered post-test counseling with the same genetic counselor who performed pre-test counseling. Test result–specific visual aids and recommendations for both positive and negative test results were used.

Telephone counseling. Women assigned to telephone counseling received counseling by a cancer genetic counselor according to the same standardized protocol as those in the in-person counseling arm. They were mailed sealed packets containing the same print materials used for in-person counseling, which were to be opened and used at the time of their telephone counseling session. Women who decided to have genetic testing were mailed a genetic test buccal kit. Post-test counseling was delivered by the same genetic counselor using the same tailored visual aids based on the results. Participants in both arms were mailed a letter summarizing their personalized risk assessment based on family history and/or genetic test result and management recommendations. Both groups were asked to identify their healthcare provider(s) to also receive the letter.

Data collection and measures. Data collectors, who were blinded to intervention assignment, collected self-reported data via telephone, Internet, or mailed surveys. Assessments were done at baseline, 1 week after pre-test and post-test counseling, 6 months, and 1 year after the last counseling session. This study focuses on 1-year outcomes.

Anxiety was measured at baseline and 1 year with the six-item state anxiety subscale of the Brief Symptom Inventory-18.[44] Higher scores indicate more anxiety (Cronbach's α coefficient = .90 to .91).

Cancer-specific distress was measured at baseline and 1 year with the 15-item Impact of Event Scale.[45] Higher scores indicate more distress (α = .89 to .90).

Mental and physical health-related quality of life was measured at baseline and 1 year with the 12-item Short Form Health Survey (SF-12, version 2).[46,47] Higher scores reflect better quality of life for the mental (α = .84) and physical (α = .88) component summary scores.

Perceived control about risk of HBOC (ie, "the problem") was assessed at 1 year with the nine-item Perceived Personal Control Questionnaire.[31] The questionnaire assesses three dimensions of control: cognitive (eg, "I feel I understand the problem that brought me to genetic counseling"), behavioral (eg, "I know what I can do to alleviate the problem"), and decisional (eg, "I feel I can make decisions that would influence future outcomes"). Higher scores indicate more perceived control (α = .85).

Decisional conflict associated with the *BRCA1/2* testing decision was measured with the 16-item version of the Decisional Conflict Scale at 1 year.[48,49] Higher scores indicate more decisional conflict (α = .92).

Decisional regret about *BRCA1/2* testing decisions were measured with the five-item Decision Regret Scale at 1 year.[50] Higher scores indicate more decisional regret (α = .91).

Risk management behaviors. Participants were provided with risk management recommendations, which were based on National Comprehensive Cancer Network guidelines and tailored to their personal cancer status, genetic test results, and presence of breast and ovaries (Appendix Table A1, online only). Counseling recommendations reflected the guidelines for surveillance at the time of the study.[51,52] Breast cancer screening, prophylactic mastectomy, and oophorectomy were assessed.[51,53]

Statistical Analysis

The a priori primary noninferiority outcomes were 1-year changes from baseline in anxiety and cancer-specific distress. Noninferiority margins reflected established clinically significant change (cancer-specific distress and decisional conflict: 4 points; mental and physical quality of life: −2.5 points).[45,46,50] In accordance with other studies and literature on meaningful changes in health,[54] a margin of no more than 0.5 standard deviation "worse" than the in-person counseling mean value was used for measures without clinical guidelines (decisional regret and anxiety: 5 points; perceived personal control: −0.2 points).

The primary noninferiority analyses were based on the available sample at baseline and 1 year.[55-57] Missing scores were substituted with estimates biased toward inferiority: substituting in-person counseling missing observations with the mean of in-person counseling, and replacing telephone counseling missing observations with the mean plus the noninferiority margin of in-person counseling. To test that telephone counseling was not unacceptably worse than in-person counseling, one-sided 97.5% cluster bootstrap CIs with 1,000 replications were used to estimate the noninferiority effects for the between-group intervention differences, while accounting for the potential correlation among subjects within the

family. The same approach was used for the exploratory analysis of the noninferiority effects for geographic (rural *v* urban) and genetic test status (tester *v* nontester) subgroups.

The equivalency of genetic testing uptake between telephone and in-person counseling within 1 year of the precounseling session was a secondary outcome. A sensitivity analysis showed that results did not differ when including or excluding women who reported testing outside the study; therefore, testing status included all women who had either study-verified testing (n = 240) or testing outside the study (n = 21). To test whether the interventions had equivalent rates of genetic testing uptake by 1 year and to exclude a potential clinically relevant difference, a two-sided 95% CI was estimated from 1,000 cluster bootstrap samples for the difference in uptake proportions (equivalence range ± 10%) for the per-protocol and intent-to-treat equivalency analyses, accounting for the correlation within families.[58] For the intent-to-treat analysis, the multiple imputation method[59,60] was used to impute the missing observations using cancer status, number of relatives with cancer, education level, and health insurance status. We also delineated risk management behaviors across the two interventions, by cancer and by genetic testing result status.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.2.1 (R Development Core Team, Vienna, Austria).

Sample Size and Power Evaluation

Sample size and power calculations were based on the trial's 6-month primary outcome analysis using NQuery Advisor 7.0.[32,61] Based on the final randomized sample size of 988, 79% retention, a mean cluster size of 1.02, and an estimated intraclass coefficient of 0.07, our ad hoc power was > 80% to detect noninferiority in cancer-specific distress and anxiety at 1 year, with an α level of 0.05.

RESULTS

Study enrollment, randomization, and retention data are shown in the CONSORT flow diagram (Fig 1). The study arms did not differ at baseline (Tables 1, 2, and 3).

Psychosocial and Informed Decision-Making Outcomes

Table 2 shows measures of psychologic distress and well-being by telephone and in-person counseling arms for the more conservative per-protocol analysis. The mean differences for participant-reported measures between the arms for noninferiority measures from baseline and 1-year follow-up values were all within the prespecified margins (Fig 2 and Table 4). No differences were observed for noninferiority based on rural versus urban residence or test uptake (Table 3), cancer cases (Appendix Table A2, online only), or uninformative and nontester result status (Appendix Table A3, online only). Results were similar for imputed data (data not shown). Missing data for these analyses ranged from 17% to 28%.

Genetic Testing

At 1 year, 27.9% of telephone counseling and 37.3% of in-person counseling participants underwent genetic testing. A 95% CI of the difference in the testing uptake was 2.2% to 16.8%, which falls outside of the equivalence range (−10% to 10%). Similar results were observed for imputed data (difference = 8.2%; 95% CI, 0.9% to 15.4%). Testing uptake was appreciably higher for rural compared with urban dwellers in both arms (rural telephone counseling: 38.7% [95% CI, 26.2% to 50.0%]; urban telephone counseling: 25.9% [95% CI, 21.1% to 30.9%]; rural in-person counseling: 41.3% [95% CI, 29.1% to 53.9%]; urban in-person counseling: 36.6% [95% CI, 30.8% to 42.8%]).

Risk Management Behaviors

Risk management behaviors based on testing status and previous cancer diagnosis are shown in Table 5. Three out of 20 women, who were *BRCA1/2* positive and had at least one breast before testing, had a prophylactic mastectomy (telephone counseling: 10% [one of 10 women]; in-person counseling: 20% [two of 10 women]). Six of 10 women ≥ 35 years old, who were *BRCA1/2* positive and had at least one ovary, underwent a prophylactic oophorectomy (telephone counseling: 50% [two of four women]; in-person counseling: 67% [four of six women]). Most women whose test results were uninformative or who did not undergo testing were up to date with breast cancer screening guidelines based on personal and family history. Significance tests were not conducted because of small subgroup sample size.

DISCUSSION

This trial provides important evidence that telephone genetic counseling for HBOC is noninferior to in-person counseling and can be delivered as safely as in-person counseling without an adverse effect on long-term psychologic, quality-of-life, and decision-making outcomes. This conclusion was robust across subgroups of participants, including those living in geographically remote areas and those choosing to be tested or not. The vast majority of participants received uninformative test results. Thus, noninferiority for women with *BRCA1/2* mutations or variants of uncertain significance cannot be certain from our data because of small subgroups.

Overall, our findings are concordant with previous research that established nonequivalency of telephone counseling up to 6 months after genetic counseling[27,32] and provide further evidence that telephone genetic counseling for HBOC can be delivered safely.[62] However, consistent with earlier reports focused on shorter-term outcomes,[27,32] at 12 months, telephone counseling continued to generate lower genetic testing rates (27.9%) than in-person counseling (37.3%) at 1 year. Reasons for this are unclear but may be due to travel time to mail test kits, a delay between telephone counseling and testing at home that might have reduced enthusiasm for testing, or the wait between telephone counseling and testing at home provided opportunity to further consider potential out-of-pocket expenses or to discuss testing with social network members. Future research is needed to better understand how counseling mode might influence testing uptake rates and whether the women at lowest risk are opting appropriately to forgo testing.

Rural women had higher test uptake rates in both the telephone and in-person counseling arms, suggesting that *BRCA1/2* testing interests were satisfied by expanding access to genetic counseling through the two modalities.[16,22,23] One explanation for this is that urban women most interested in testing may have had access to genetic testing before the study. Many urban women may have been tested and were therefore not eligible for the trial. Thus,

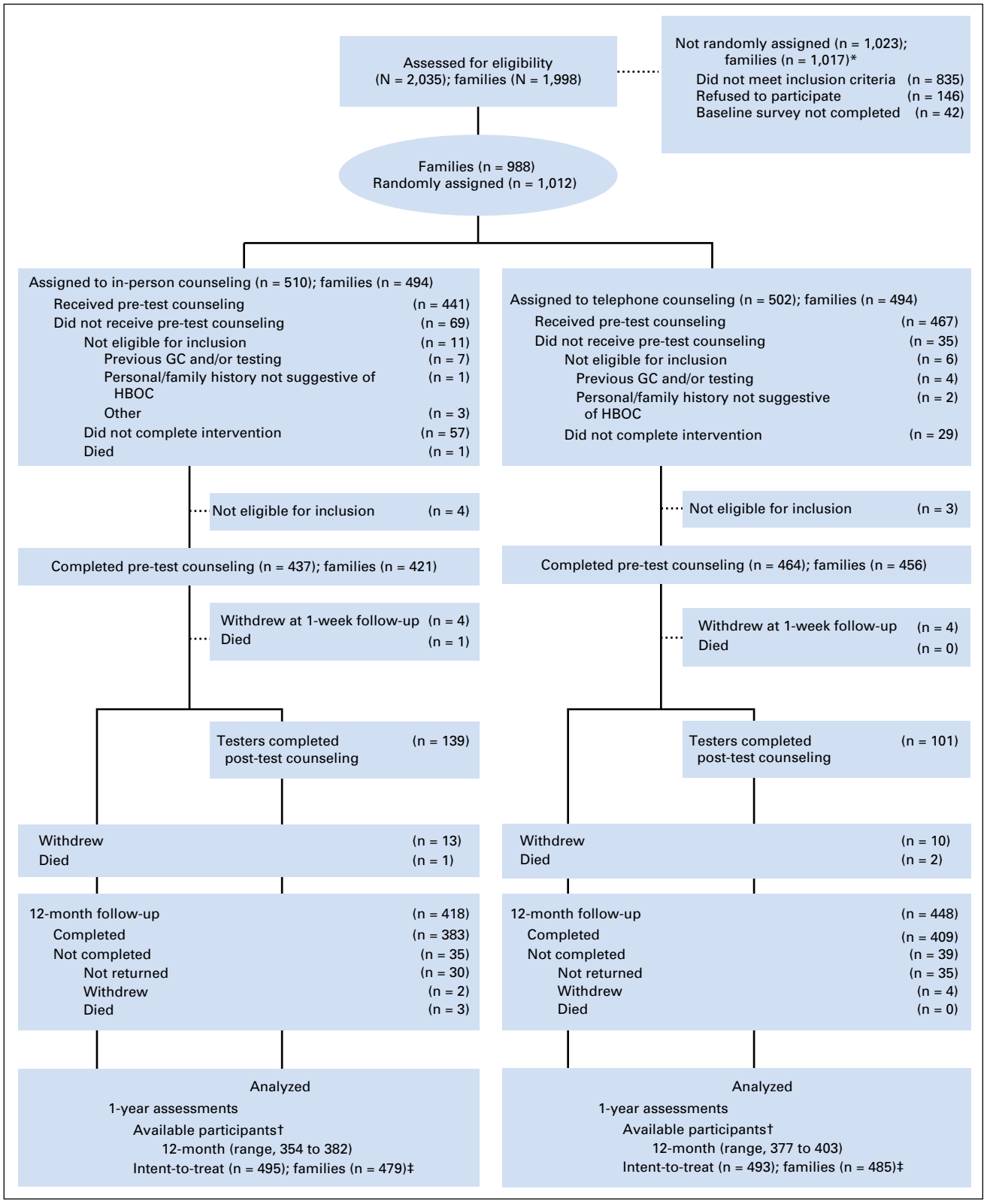

Fig 1. CONSORT diagram. *Seven families had at least one member randomly assigned and one member not randomly assgned. †Total number of participants depends on completion of intervention and completion of measure. ‡Intent-to-treat refers to data analysis after imputation of unknown testing uptake. GC, genetic counseling; HBOC, hereditary breast and ovarian cancer.

Table 1. Characteristics by Overall Sample and by Intervention Group

Characteristic	Overall, % (No.; N = 988)	Telephone, % (No.; n = 493)	In Person, % (No.; n = 495)
Age, years			
Mean ± SD	56.1 ± 8.2	56.2 ± 8.1	55.9 ± 8.3
Self-reported race/ethnicity			
Non-Hispanic white	94.1 (930)	95.7 (472)	92.5 (458)
Hispanic	3.2 (32)	2.0 (10)	4.4 (22)
Other	2.6 (26)	2.2 (11)	3.0 (15)
Self-reported Ashkenazi Jewish ancestry			
Yes	0.9 (9)	1.2 (6)	0.6 (3)
No	99.1 (979)	98.8 (487)	99.4 (492)
Marital status			
Married or living as married	79.3 (784)	80.1 (395)	78.6 (389)
Single/widowed/separated/divorced	20.6 (204)	19.9 (98)	21.4 (106)
Educational level			
High school or less	21.8 (215)	23.5 (116)	20.0 (99)
Some college, associates degree, or vocational school	37.9 (374)	34.3 (169)	41.4 (205)
Bachelor's degree or higher	40.4 (399)	42.2 (208)	38.6 (191)
Rural *v* urban residence*			
Urban	85.4 (844)	84.8 (418)	86.1 (426)
Rural	14.6 (144)	15.2 (75)	13.9 (69)
Yearly household income, $			
≤ 29,999	13.0 (128)	14.0 (69)	11.9 (59)
30,000-49,999	19.2 (190)	17.0 (84)	21.4 (106)
50,000-69,999	19.0 (188)	19.1 (94)	19.0 (94)
≥ 70,000	45.0 (445)	44.8 (221)	45.3 (224)
Missing data	3.7 (37)	5.1 (25)	2.4 (12)
Employment status			
Employed (for wages or self-employed)	62.0 (613)	61.1 (301)	63.0 (312)
Not employed	38.0 (375)	38.9 (192)	37.0 (183)
Health care coverage			
Yes	96.9 (957)	95.5 (471)	98.2 (486)
No	3.1 (31)	4.5 (22)	1.8 (9)
Has a personal health care provider			
Yes	88.7 (876)	88.6 (437)	88.7 (439)
No	11.3 (112)	11.4 (56)	11.3 (56)
Personal history of breast and/or ovarian/fallopian tube/ peritoneal cancer			
Yes	97.6 (964)	98.4 (485)	96.8 (479)
No	2.4 (24)	1.6 (8)	3.2 (16)
Recruited relatives of *BRCA1/2* carriers			
Yes	2.5 (25)	1.6 (8)	3.4 (17)
No	97.5 (963)	98.4 (485)	96.6 (478)
Number of first- and second-degree relatives with breast or ovarian cancer			
0 FDR and 0 SDR	52.2 (516)	51.9 (256)	52.5 (260)
1 FDR or 1 SDR	27.8 (275)	26.6 (131)	29.1 (144)
2 or more FDR/SDR	19.9 (197)	21.5 (106)	18.4 (91)

Abbreviations: FDR, first-degree relative; SDR, second-degree relative.

*Rural or urban residence was based on Rural-Urban Commuting Area (RUCA) codes at the zip code level. RUCA codes were developed by the University of Washington Rural Health Research Center and the United States Department of Agriculture Economic Research Service (ERS), with the support of the federal Health Resource and Service Administration's Office of Rural Health Policy and the ERS, using standard Census Bureau urbanized area and urban cluster definitions in combination with work commuting data to characterize census tracts and then zip codes. The 10 RUCA categories were aggregated into urban (1 to 3) and rural (4 to 10), as recommended by the WWAMI (Washington, Wyoming, Alaska, Montana, and Idaho) Rural Health Research Center.

the urban sample may have been biased toward women who were less interested in testing. Nonetheless, the rates of testing in our study are substantially lower than in other studies where women who were members of families with a known deleterious mutation[27,63,64] were self- or physician-referred, but similar to a study of African American women.[65]

A contributing factor to the lower overall uptake of testing in this study may be the active recruitment strategy, which identified eligible women from population-based sources without any direct involvement of or referral from their primary health care providers. In general, recommendations from a health care provider strengthen perceptions about the importance of recommendations.[66] Outcomes of telephone and in-person genetic counseling will likely be optimal when integrated into the health care system and the messages are supported and reinforced by the patient's entire health care team.

To our knowledge, our study is the first to assess risk management outcomes at 1 year after telephone and in-person counseling. The majority of women adhered to screening clinical breast examination and mammography guidelines (although not for breast magnetic resonance imaging [MRI]). Uptake of breast MRI was low, but during the timeframe of the study, guidelines for use of breast MRI only addressed at-risk individuals, and there were no formal guidelines recommending breast MRI

Table 2. Noninferiority of Telephone to In Person Counseling on Psychosocial, Quality-of-Life, and Informed Decision–Making Outcomes by Intervention Arm: 1-Year Follow-Up

	Baseline						1-Year Follow-Up						1-Year Change From Baseline					
	Overall		Telephone		In Person		Overall		Telephone		In Person		Overall		Telephone		In Person	
Outcome	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)	No. of Participants	Mean Score (95% CI)
Anxiety (possible scores range from 0 to 24)	988	2.69 (2.50 to 2.88)	493	2.76 (2.49 to 3.05)	495	2.61 (2.36 to 2.88)	785	2.56 (2.34 to 2.77)	403	2.74 (2.42 to 3.09)	382	2.37 (2.08 to 2.67)	785	−0.05 (−0.24 to 0.13)	403	−0.01 (−0.26 to 0.24)	382	−0.09 (−0.35 to 0.18)
Cancer-specific distress (possible scores range from 0 to 75)	981	15.43 (14.52 to 16.35)	490	15.41 (14.21 to 16.62)	491	15.45 (14.22 to 16.80)	770	10.64 (9.68 to 11.56)	397	11.19 (9.91 to 12.52)	373	10.06 (8.81 to 11.34)	764	−4.09 (−4.92 to −3.31)	395	−3.77 (−4.84 to −2.69)	369	−4.43 (−5.66 to −3.19)
Quality of life: physical health (possible scores range from 0 to 100)	985	49.61 (49.03 to 50.17)	491	49.55 (48.74 to 50.34)	494	49.67 (48.82 to 50.47)	776	50.14 (49.44 to 50.83)	397	49.75 (48.74 to 50.65)	379	50.54 (49.61 to 51.52)	776	−0.20 (−0.70 to 0.32)	397	−0.39 (−1.10 to 0.32)	379	0 (−0.62 to 0.65)
Quality of life: mental health (possible scores range from 0 to 100)	985	51.13 (50.57 to 51.70)	491	51.34 (50.50 to 52.14)	494	50.91 (50.14 to 51.70)	776	50.63 (49.95 to 51.29)	397	50.74 (49.77 to 51.70)	379	50.51 (49.60 to 51.41)	776	−0.93 (−1.49 to −0.35)	397	−0.79 (−1.58 to 0.04)	379	−1.09 (−1.90 to −0.23)
Decisional conflict (possible scores range from 0 to 100)							734	26.82 (25.70 to 27.95)	379	26.76 (25.19 to 28.38)	355	26.88 (25.32 to 28.62)						
Decisional regret (possible scores range from 0 to 100)							731	21.22 (19.96 to 22.50)	377	21.07 (19.25 to 22.82)	354	21.38 (19.52 to 23.30)						
Perceived personal control (possible scores range from 0 to 2)							786	1.53 (1.50 to 1.55)	405	1.52 (1.49 to 1.56)	381	1.53 (1.49 to 1.57)						

Table 3. Noninferiority of Telephone to In-Person Counseling on Informed Decision Making and Change Between Baseline and 1-Year Follow-Up of Psychosocial and Quality-of-Life Outcomes by Intervention Arm and Urban Versus Rural, Tester Versus Nontester Groups

	Urban					Rural					Tester					Nontester				
	Telephone		In Person		Difference, Telephone − In Person	Telephone		In Person		Difference, Telephone − In Person	Telephone		In Person		Difference, Telephone − In Person	Telephone		In Person		Difference, Telephone − In Person
Outcome	No. of Participants	Mean (95% CI)	No. of Participants	Mean (95% CI)	Mean (95% CI)	No. of Participants	Mean (95% CI)	No. of Participants	Mean (95% CI)	Mean (95% CI)	No. of Participants	Mean (95% CI)	No. of Participants	Mean (95% CI)	Mean (95% CI)	No. of Participants	Mean (95% CI)	No. of Participants	Mean (95% CI)	Mean (95% CI)
Anxiety*	344	−0.03 (−0.32 to 0.22)	321	0.00 (−0.30 to 0.30)	−0.03 (−0.72 to 0.30)	59	0.10 (−0.59 to 0.76)	61	−0.54 (−1.17 to 0.13)	0.64 (−0.85 to 1.37)	105	0.16 (−0.22 to 0.56)	130	−0.45 (−0.85 to −0.01)	0.61 (−0.30 to 1.09)	291	−0.12 (−0.41 to 0.20)	247	0.08 (−0.25 to 0.47)	−0.19 (−0.93 to 0.19)
Cancer-specific distress*	337	−3.47 (−4.64 to −2.30)	310	−4.21 (−5.53 to −2.80)	0.74 (−2.30 to 2.15)	58	−5.55 (−8.90 to −2.17)	59	−5.59 (−8.95 to −2.61)	0.04 (−6.70 to 4.05)	102	−4.80 (−6.80 to −2.76)	124	−4.50 (−6.60 to −2.53)	−0.30 (−5.35 to 2.00)	286	−3.59 (−4.82 to −2.24)	240	−4.63 (−6.14 to −3.07)	1.04 (−2.24 to 2.81)
Quality of life: physical health*	339	−0.29 (−1.06 to 0.51)	318	0.20 (−0.45 to 0.89)	−0.49 (−1.36 to 1.29)	58	−1.02 (−2.81 to 0.94)	61	−1.05 (−2.90 to 0.78)	0.03 (−2.21 to 4.59)	104	−0.67 (−2.28 to 0.82)	129	−0.56 (−1.84 to 0.59)	−0.11 (−1.73 to 3.36)	286	−0.24 (−1.11 to 0.53)	245	0.27 (−0.50 to 1.02)	−0.51 (−1.51 to 1.18)
Quality of life: mental health*	339	−0.88 (−1.75 to 0.06)	318	−1.17 (−2.07 to −0.23)	0.29 (−0.80 to 2.30)	58	−0.23 (−2.17 to 1.74)	61	−0.65 (−2.35 to 0.98)	0.42 (−1.66 to 5.39)	104	−0.26 (−1.92 to 1.34)	129	−0.18 (−1.50 to 1.33)	−0.08 (−1.95 to 3.14)	286	−0.89 (−1.91 to −0.02)	245	−1.45 (−2.54 to −0.47)	0.56 (−0.55 to 2.61)
Decisional conflict	325	27.25 (25.46 to 29.05)	300	26.41 (24.70 to 28.10)	0.84 (−3.00 to 3.06)	54	23.80 (20.00 to 27.81)	55	29.42 (25.23 to 33.59)	−5.62 (−14.98 to −0.88)	103	17.43 (14.63 to 20.53)	120	22.62 (19.88 to 25.70)	−5.19 (−11.29 to −2.05)	270	30.37 (28.54 to 32.25)	231	29.16 (27.38 to 30.97)	1.21 (−2.76 to 3.35)
Decisional regret	323	21.53 (19.45 to 23.57)	300	21.34 (19.10 to 23.52)	0.19 (−4.89 to 2.69)	54	18.33 (13.60 to 23.35)	54	21.57 (17.24 to 25.79)	−3.24 (−15.70 to 2.215)	103	10.73 (8.08 to 13.44)	120	12.58 (9.81 to 15.69)	−1.86 (−9.04 to 1.22)	268	25.20 (22.94 to 27.48)	230	25.95 (23.69 to 28.29)	−0.74 (−6.25 to 2.01)
Perceived personal control	345	1.52 (1.48 to 1.56)	320	1.54 (1.50 to 1.58)	−0.02 (−0.06 to 0.06)	60	1.53 (1.44 to 1.63)	61	1.49 (1.38 to 1.61)	0.04 (−0.08 to 0.26)	107	1.62 (1.57 to 1.69)	131	1.63 (1.57 to 1.69)	−0.01 (−0.08 to 0.16)	291	1.48 (1.43 to 1.52)	245	1.48 (1.43 to 1.52)	0.00 (−0.05 to 0.12)

*Values indicate change from baseline.

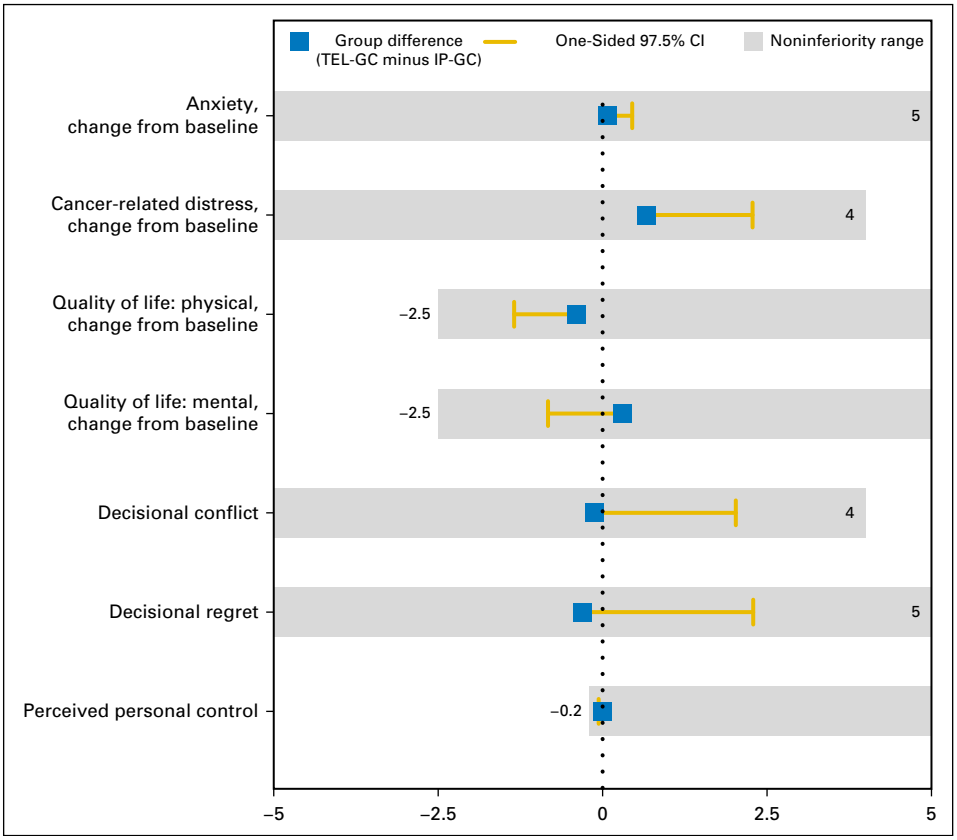

Fig 2. Effects and noninferiority ranges 1 year after the last intervention. GC, genetic counseling; IP, in person; TEL, telephone.

for ongoing screening for cancer survivors. Most *BRCA1/2* carriers ≥ 35 years old had a bilateral salpingo-oophorectomy, but only one carrier had a prophylactic mastectomy. Available evidence indicates that women undergo risk-reducing surgeries over time, well beyond the first year.[67,68] Thus, longer-term assessments of risk management behaviors and decision-making factors postcounseling require further study.

The study's results have implications for care delivery and policy. Noninferiority of telephone counseling at 1 year provides additional evidence that telephone-delivered genetic counseling and testing could expand access to *BRCA1/2* counseling. Telephone counseling can improve access from geographically remote areas, ease the travel and care burden for patients traveling to a clinic, and increase perceived control when patients are given a choice about their preferred counseling mode. It can also address the limited genetic counseling work force as the demand for clinical genetic services increases.[20,69] However, it is not clear whether telephone counseling is noninferior for women who test *BRCA1/2* positive, have variants of uncertain significance, and seek multigene testing. Furthermore, telephone counseling strategies would have to be reassessed in the general population in women without a previous diagnosis of cancer.

National best practice guidelines recommend that trained cancer genetic professionals provide comprehensive cancer genetics risk assessment to women who meet testing criteria. However, it is estimated that less than one-third of these women receive genetic counseling.[29,30,66] During our recruitment process, we observed low rates of prior counseling and testing utilization by women with a personal history of cancer (30%), providing additional evidence for low rates of accessing genetic counseling and

Table 4. Noninferiority of Telephone Counseling to In-Person Counseling on Psychosocial, Quality-of-Life, and Informed Decision–Making Outcomes Per-Protocol Analysis

Outcome	Mean Difference	97.5% CI	Noninferiority Margin*
Anxiety	0.08	−0.52 to 0.45	5
Cancer-specific distress	0.66	−1.75 to 2.28	4
Quality of life: physical health	−0.39	−1.35 to 1.06	−2.5
Quality of life: mental health	0.30	−0.83 to 2.26	−2.5
Decisional conflict	−0.12	−3.69 to 2.03	4
Decisional regret	−0.31	−4.25 to 2.29	5
Perceived personal control	−0.01	−0.06 to 0.06	−0.2

*A noninferiority test tests that the telephone counseling mean is not worse than the in-person counseling mean (as the reference mean) by more than the prespecified noninferiority margin.

Table 5. Breast and Ovarian Cancer Risk Management* by *BRCA1/2* Testing Status and Intervention Arm at 1-Year Follow-Up

Cancer Case/Relative	Test Status	Screening by Guideline Recommended Age	No. of Participants†	Overall	In Person	Telephone
Previous cancer diagnosis						
	BRCA1/2 positive (n = 16)				(n = 6)	(n = 8)
		CBE (> 25 years old)	14	11 (78.6%)	6 (100%)	5 (62.5%)
		Mammogram (> 25 years old)	14	10 (71.4%)	6 (100%)	4 (50.0%)
		Breast MRI (> 25 years old)	14	7 (50.0%)	3 (50.0%)	4 (50.0%)
		PM	14	1 (7.1%)	0 (0%)	1 (12.5%)
	(n = 7)	PO (≥ 35 years old)	7	5 (71.4%)	3 of 3 (100%)	2 of 4 (50.0%)
	(n = 0)	PO (< 35 years old)	0	0 (0%)	0 (0%)	0 (0%)
	BRCA1/2 negative‡ (n = 2)				(n = 1)	(n = 1)
		CBE	2	1 (50.0%)	1 (100%)	0 (0%)
		Mammogram	2	1 (50.0%)	1 (100%)	0 (0%)
		Breast MRI	2	0 (0%)	0 (0%)	0 (0%)
	Uninformative§ (n = 191)				(n = 82)	(n = 74)
		CBE	156	132 (84.6%)	70 (85.4%)	62 (83.8%)
		Mammogram	156	133 (85.3%)	71 (86.6%)	62 (83.8%)
		Breast MRI	156	10 (6.4%)	5 (6.1%)	5 (6.8%)
	Nontester (n = 492)				(n = 198)	(n = 226)
		CBE	424	375 (88.4%)	178 (89.9%)	197 (87.2%)
		Mammogram	424	377 (88.9%)	177 (89.4%)	200 (88.5%)
		Breast MRI	424	15 (3.5%)	4 (2.0%)	11 (4.9%)
Unaffected at-risk relative						
	BRCA1/2 positive (n = 6)				(n = 4)	(n = 2)
		CBE (> 25 years old)	6	3 (50.0%)	2 (50.0%)	1 (50.0%)
		Mammogram (> 25 years old)	6	2 (33.3%)	1 (25.0%)	1 (50.0%)
		Breast MRI (> 25 years old)	6	1 (16.7%)	1 (25.0%)	0 (0%)
		PM	6	2 (33.3%)	2 (50.0%)	0 (0%)
		Chemoprevention	6	0 (0%)	0 (0%)	0 (0%)
	(n = 4)	PO (≥ 35 years old)	3	1 (33.3%)	1 of 3 (33.3%)	0 of 0 (0%)
	(n = 3)	PO (< 35 years old)	2	0 (0%)	0 of 0 (0%)	0 of 2 (0%)
	BRCA1/2 negative				(n = 4)	(n = 3)
	(n = 9)	CBE (≥ 40 years old)	7	7 (100%)	4 (100%)	3 (100%)
		Mammogram (≥ 40 years old)	7	7 (100%)	4 (100%)	3 (100%)
					(n = 2)	(n = 1)
	(n = 4)	CBE (< 40 years old)	3	2 (66.7%)	2 (100%)	0 (0%)
		Mammogram (< 40 years old)	3	1 (33.3%)	1 (50.0%)	0 (0%)
	Nontester (n = 2)				(n = 1)	(n = 1)
		CBE (> 25 years old)	2	1 (50.0%)	0 (0%)	1 (100%)
		Mammogram (> 25 years old)	2	0 (0%)	0 (0%)	0 (0%)
		Breast MRI (> 25 years old)	2	0 (0%)	0 (0%)	0 (0%)
		PM	2	0 (0%)	0 (0%)	0 (0%)
		Chemoprevention	2	0 (0%)	0 (0%)	0 (0%)
	(n = 0)	PO (≥ 35 years old)	0	0 (0%)	0 of 0 (0%)	0 of 0 (0%)
	(n = 2)	PO (< 35 years old)	2	0 (0%)	0 of 1 (0%)	0 of 1 (0%)

NOTE. Percent of participants younger than 40 years of age are as follows: cancer case, seven of 701 participants (1%); at-risk relative, 12 of 21 participants (57%).
Abbreviations: CBE, clinical breast examination; MRI, magnetic resonance imaging; PM, prophylactic mastectomy; PO, prophylactic oophorectomy.
*Those included in the analysis reported that at least one breast or ovary was present at baseline; age-eligible women were considered for specific screening and prophylactic surgery outcomes.
†These numbers include only those who responded to the baseline and the 6- and/or 12-month surveys.
‡Test result negative is defined as a person who tested negative for a known mutation.
§Test result uninformative is defined as no pathogenic mutation identified in the family, and the cause of the cancer risk remains unknown.

testing. To our knowledge, our population-based recruitment approach to deliver remote cancer genetic services is unprecedented. It is noteworthy that the Utah Cancer Registry was able to contact 91.5% of potentially eligible cancer survivors, and 89.8% of eligible survivors who were invited to participate in the study accepted genetic counseling. Cancer registries have primarily focused on collecting epidemiologic data. Our study exemplifies how cancer registries can help implement health promotion interventions with survivors and their at-risk family members. Furthermore, patient contact through registries may be an effective public health strategy for expanding access to telephone counseling at a lower cost than in-person counseling[27,28] to large numbers of people who may benefit from such services.[70-73] Involving patients' providers, especially in follow-up of test results and recommendations, is likely to maximize program effectiveness.

Recent discussions about population-wide *BRCA* testing have been spurred by new findings that it is not uncommon for *BRCA1* and *BRCA2* mutations to be identified in individuals without a clear indication for testing. Recent estimates suggest that population screening would identify a mutation in approximately one in 300 women.[74,75] Evidence-based alternative counseling models, such as telephone counseling, could be implemented as part of comprehensive precision cancer prevention approaches that involve genetic testing.

Our study had several limitations. Because our sample was from a single state, was largely non-Hispanic white, and had a personal history of cancer, our study may have limited generalizability. Furthermore, our findings may be generalizable only to settings where patients are counseled by board-certified genetic counselors because adherence to best practices differs by provider type.[17,76] The small number of women who obtained genetic testing limits our ability to draw meaningful conclusions about the noninferiority of telephone counseling for risk management outcomes. Our sample may not be representative of patients who are physician- or self-referred for genetic counseling/testing, or who are referred for urgent testing to help make immediate treatment decisions. The small number of mutation carriers limited our ability to draw meaningful conclusions about uptake of prophylactic surgeries. We did not assess behavioral intent to undergo surveillance or prophylactic surgery. Finally, our results may not be generalizable to rapidly evolving multigene panel testing, which poses challenges for risk communication, especially given uncertainties about cancer risks and medical management.[77]

In conclusion, this study provides strong long-term evidence that telephone counseling for women at risk of HBOC is not inferior to in-person counseling with regard to fostering informed decision making, minimizing adverse psychologic and quality-of-life outcomes, and promoting perceived personal control 1 year after counseling. Alternative care delivery approaches, such as telephone communication, can make cancer genetic services more widely accessible without sacrificing safety.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Anita Y. Kinney, Wendy Kohlmann, Jeanne S. Mandelblatt, Marc D. Schwartz
Administrative support: Wendy Kohlmann, Antoinette M. Stroup
Provision of study materials or patients: Wendy Kohlmann, Antoinette M. Stroup
Collection and assembly of data: Anita Y. Kinney, Wendy Kohlmann, Saundra S. Buys, Antoinette M. Stroup, Rebecca A. Campo
Data analysis and interpretation: Anita Y. Kinney, Laurie E. Steffen, Barbara H. Brumbach, Wendy Kohlmann, Ruofei Du, Ji-Hyun Lee, Amanda Gammon, Karin Butler, Kristina G. Flores, Jeanne S. Mandelblatt
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Claus EB, Schildkraut JM, Thompson WD, et al: The genetic attributable risk of breast and ovarian cancer. Cancer 77:2318-2324, 1996
2. Couch FJ, DeShano ML, Blackwood MA, et al: BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 336: 1409-1415, 1997
3. Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 62:676-689, 1998
4. Frank TS, Critchfield GC: Hereditary risk of women's cancers. Best Pract Res Clin Obstet Gynaecol 16:703-713, 2002
5. Martin AM, Blackwood MA, Antin-Ozerkis D, et al: Germline mutations in BRCA1 and BRCA2 in breast-ovarian families from a breast cancer risk evaluation clinic. J Clin Oncol 19:2247-2253, 2001
6. Spitzer E, Abbaszadegan MR, Schmidt F, et al: Detection of BRCA1 and BRCA2 mutations in breast cancer families by a comprehensive two-stage screening procedure. Int J Cancer 85: 474-481, 2000
7. Kadouri L, Hubert A, Rotenberg Y, et al: Cancer risks in carriers of the BRCA1/2 Ashkenazi founder mutations. J Med Genet 44:467-471, 2007
8. Finch A, Beiner M, Lubinski J, et al: Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. JAMA 296:185-192, 2006
9. Mavaddat N, Peock S, Frost D, et al: Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. J Natl Cancer Inst 105:812-822, 2013
10. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91:1310-1316, 1999
11. Cohen SA, Marvin ML, Riley BD, et al: Identification of genetic counseling service delivery models in practice: A report from the NSGC Service Delivery Model Task Force. J Genet Couns 22: 411-421, 2013
12. Madlensky L: Is it time to embrace telephone genetic counseling in the oncology setting? J Clin Oncol 32:611-612, 2014
13. Levy-Lahad E, Lahad A, King MC: Precision medicine meets public health: Population screening for BRCA1 and BRCA2. J Natl Cancer Inst 107:420, 2014
14. Pal T, Lee JH, Besharat A, et al: Modes of delivery of genetic testing services and the uptake of cancer risk management strategies in BRCA1 and BRCA2 carriers. Clin Genet 85:49-53, 2014
15. Scheuner MT, Sieverding P, Shekelle PG: Delivery of genomic medicine for common chronic adult diseases: A systematic review. JAMA 299: 1320-1334, 2008
16. Trivers KF, Baldwin LM, Miller JW, et al: Reported referral for genetic counseling or BRCA 1/2 testing among United States physicians: A vignette-based study. Cancer 117:5334-5343, 2011
17. Cragun D, Camperlengo L, Robinson E, et al: Differences in BRCA counseling and testing practices based on ordering provider type. Genet Med 17: 51-57, 2015
18. Nelson HD, Pappas M, Zakher B, et al: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: A systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med 160:255-266, 2014
19. Moyer VA; U.S. Preventive Services Task Force: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 160:271-281, 2014
20. Acheson LS, Stange KC, Zyzanski S: Clinical genetics issues encountered by family physicians. Genet Med 7:501-508, 2005
21. Brandt R, Ali Z, Sabel A, et al: Cancer genetics evaluation: Barriers to and improvements for referral. Genet Test 12:9-12, 2008
22. D'Agincourt-Canning L: Genetic testing for hereditary cancer: Challenges to ethical care in rural and remote communities. HEC Forum 16:222-233, 2004
23. Fineman RM, Doyle DL: Public health needs assessment for state-based genetic services delivery, in Khoury MJ, Burke W, Thomson E (eds): Genetics and Public Health in the 21st Century. Oxford, United Kingdom, Oxford University Press, 2000, pp 261-272
24. Vadaparampil ST, Wideroff L, Breen N, et al: The impact of acculturation on awareness of genetic testing for increased cancer risk among Hispanics in the year 2000 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev 15:618-623, 2006
25. Wideroff L, Vadaparampil ST, Breen N, et al: Awareness of genetic testing for increased cancer risk in the year 2000 National Health Interview Survey. Community Genet 6:147-156, 2003
26. Anderson B, McLosky J, Wasilevich E, et al: Barriers and facilitators for utilization of genetic counseling and risk assessment services in young female breast cancer survivors. J Cancer Epidemiol 2012:298745, 2012
27. Schwartz MD, Valdimarsdottir HB, Peshkin BN, et al: Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. J Clin Oncol 32:618-626, 2014
28. Chang Y, Near AM, Butler KM, et al: Economic evaluation alongside a clinical trial of telephone versus in-person genetic counseling for BRCA1/2 mutations in geographically underserved areas. J Oncol Pract 12:59-e1-e13, 2016
29. Mackenzie A, Patrick-Miller L, Bradbury AR: Controversies in communication of genetic risk for hereditary breast cancer. Breast J 15:S25-S32, 2009 (suppl 1)

30. Burgess KR, Carmany EP, Trepanier AM: A comparison of telephone genetic counseling and in-person genetic counseling from the genetic counselor's perspective. J Genet Couns 25:112-126, 2016

31. Smets EMA, Pieterse AH, Aalfs CM, et al: The perceived personal control (PPC) questionnaire as an outcome of genetic counseling: Reliability and validity of the instrument. Am J Med Genet A 140: 843-850, 2006

32. Kinney AY, Butler KM, Schwartz MD, et al: Expanding access to BRCA1/2 genetic counseling with telephone delivery: A cluster randomized trial. J Natl Cancer Inst 106:dju328, 2014

33. Butow PN, Lobb EA, Meiser B, et al: Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: A systematic review. Med J Aust 178:77-81, 2003

34. Heiniger L, Butow PN, Price MA, et al: Distress in unaffected individuals who decline, delay or remain ineligible for genetic testing for hereditary diseases: A systematic review. Psychooncology 22: 1930-1945, 2013

35. Hirschberg AM, Chan-Smutko G, Pirl WF: Psychiatric implications of cancer genetic testing. Cancer 121:341-360, 2015

36. Meiser B, Halliday JL: What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Soc Sci Med 54:1463-1470, 2002

37. Schwartz MD, Peshkin BN, Hughes C, et al: Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. J Clin Oncol 20:514-520, 2002

38. van Dijk S, Timmermans DR, Meijers-Heijboer H, et al: Clinical characteristics affect the impact of an uninformative DNA test result: The course of worry and distress experienced by women who apply for genetic testing for breast cancer. J Clin Oncol 24: 3672-3677, 2006

39. Watson M, Lloyd S, Davidson J, et al: The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. Br J Cancer 79:868-874, 1999

40. Hurdle JF, Haroldsen SC, Hammer A, et al: Identifying clinical/translational research cohorts: Ascertainment via querying an integrated multi-source database. J Am Med Inform Assoc 20:164-171, 2013

41. Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 4.2013, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Fort Washington, PA, National Comprehensive Cancer Network, 2013

42. Peshkin BN, Demarco TA, Graves KD, et al: Telephone genetic counseling for high-risk women undergoing BRCA1 and BRCA2 testing: Rationale and development of a randomized controlled trial. Genet Test 12:37-52, 2008

43. Trepanier A, Ahrens M, McKinnon W, et al: Genetic cancer risk assessment and counseling: Recommendations of the National Society of Genetic Counselors. J Genet Couns 13:83-114, 2004

44. Derogatis LR. BSI 18 Brief Symptom Inventory 18: Administration, Scoring, and Procedures Manual. NCS Pearson, Inc., Minneapolis, MN. 2000

45. Horowitz M, Wilner N, Alvarez W: Impact of Event Scale: A measure of subjective stress. Psychosom Med 41:209-218, 1979

46. Ware J, Jr, Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Med Care 34:220-233, 1996

47. Ware JE, Jr: SF-36 health survey update. Spine 25:3130-3139, 2000

48. O'Connor AM: Validation of a decisional conflict scale. Med Decis Making 15:25-30, 1995

49. O'Connor AM: User Manual - Decisional Conflict Scale. Ottawa, Canada, Ottawa Hospital Research Institute, 1993

50. O'Connor AM: User Manual - Decision Regret Scale. Ottawa, Canada, University of Ottawa, 1996

51. Breast Cancer Screening and Diagnosis Version 1.2012, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Fort Washington, PA, National Comprehensive Cancer Network, 2012

52. Daly MB, Pilarski R, Axilbund JE, et al: Genetic/familial high-risk assessment: Breast and ovarian, version 1.2014. J Natl Compr Canc Netw 12: 1326-1338, 2014

53. Moyer VA; U.S. Preventive Services Task Force: Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 157:900-904, 2012

54. Norman GR, Sloan JA, Wyrwich KW: Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care 41:582-592, 2003

55. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials, E9. Current Step 4 version, February 5, 1998. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

56. Le Henanff A, Giraudeau B, Baron G, et al: Quality of reporting of noninferiority and equivalence randomized trials. JAMA 295:1147-1151, 2006

57. Piaggio G, Elbourne DR, Pocock SJ, et al: Reporting of noninferiority and equivalence randomized trials: Extension of the CONSORT 2010 statement. JAMA 308:2594-2604, 2012

58. Efron B, Tibshirani R. An Introduction to the Bootstrap. Chapman & Hall/CRC, Boca Raton, FL. 1993

59. Rubin DB: Inference and missing data. Biometrika 63:581-592, 1976

60. Rubin DB. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, Inc., Hoboken, NJ. 1987

61. Elashoff JD: nQuery Advisor Version 7.0 User's Guide. Los Angeles, CA, Statistical Solutions Ltd, 2007

62. Doughty Rice C, Ruschman JG, Martin LJ, et al: Retrospective comparison of patient outcomes after in-person and telephone results disclosure counseling for BRCA1/2 genetic testing. Fam Cancer 9: 203-212, 2010

63. Kinney AY, Simonsen SE, Baty BJ, et al: Acceptance of genetic testing for hereditary breast ovarian cancer among study enrollees from an African American kindred. Am J Med Genet A 140: 813-826, 2006

64. Botkin JR, Smith KR, Croyle RT, et al: Genetic testing for a BRCA1 mutation: Prophylactic surgery and screening behavior in women 2 years post testing. Am J Med Genet A 118A:201-209, 2003

65. Halbert CH, Kessler L, Stopfer JE, et al: Low rates of acceptance of BRCA1 and BRCA2 test results among African American women at increased risk for hereditary breast-ovarian cancer. Genet Med 8:576-582, 2006

66. Armstrong J, Toscano M, Kotchko N, et al: Utilization and Outcomes of BRCA Genetic Testing and Counseling in a National Commercially Insured Population: The ABOUT Study. JAMA Oncol 1: 1251-1260, 2015

67. Metcalfe KA, Mian N, Enmore M, et al: Long-term follow-up of Jewish women with a BRCA1 and BRCA2 mutation who underwent population genetic screening. Breast Cancer Res Treat 133:735-740, 2012

68. Schwartz MD, Isaacs C, Graves KD, et al: Long-term outcomes of BRCA1/BRCA2 testing: Risk reduction and surveillance. Cancer 118:510-517, 2012

69. Vig HS, Armstrong J, Egleston BL, et al: Cancer genetic risk assessment and referral patterns in primary care. Genet Test Mol Biomarkers 13: 735-741, 2009

70. Carpentier MY, Tiro JA, Savas LS, et al: Are cancer registries a viable tool for cancer survivor outreach? A feasibility study. J Cancer Surviv 7: 155-163, 2013

71. Kinney AY, Boonyasiriwat W, Walters ST, et al: Telehealth personalized cancer risk communication to motivate colonoscopy in relatives of patients with colorectal cancer: The family CARE Randomized controlled trial. J Clin Oncol 32:654-662, 2014

72. Lowery JT, Axell L, Vu K, et al: A novel approach to increase awareness about hereditary colon cancer using a state cancer registry. Genet Med 12: 721-725, 2010

73. Lowery JT, Horick N, Kinney AY, et al: A randomized trial to increase colonoscopy screening in members of high-risk families in the colorectal cancer family registry and cancer genetics network. Cancer Epidemiol Biomarkers Prev 23:601-610, 2014

74. Gabai-Kapara E, Lahad A, Kaufman B, et al: Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci USA 111:14205-14210, 2014

75. Manchanda R, Legood R, Burnell M, et al: Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history-based testing. J Natl Cancer Inst 107:380, 2014

76. Vadaparampil ST, Scherr CL, Cragun D, et al: Pre-test genetic counseling services for hereditary breast and ovarian cancer delivered by non-genetics professionals in the state of Florida. Clin Genet 87: 473-477, 2015

77. Easton DF, Pharoah PD, Antoniou AC, et al: Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 372:2243-2257, 2015

Affiliations

Anita Y. Kinney, Laurie E. Steffen, Barbara H. Brumbach, Ruofei Du, Ji-Hyun Lee, Karin Butler, and Kristina G. Flores, University of New Mexico, Albuquerque, NM; Wendy Kohlmann, Amanda Gammon, and Saundra S. Buys, University of Utah, Salt Lake City, UT; Antoinette M. Stroup, Rutgers, The State University of New Jersey, New Brunswick, NJ; Rebecca A. Campo, University of North Carolina at Chapel Hill, Chapel Hill, NC; and Jeanne S. Mandelblatt and Marc D. Schwartz, Georgetown University, Washington, DC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Noninferiority Trial of Telephone Delivery of *BRCA1/2* Genetic Counseling Compared With In-Person Counseling: 1-Year Follow-Up

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Anita Y. Kinney
No relationship to disclose

Laurie E. Steffen
No relationship to disclose

Barbara H. Brumbach
No relationship to disclose

Wendy Kohlmann
Honoraria: Myriad Genetics
Consulting or Advisory Role: Myriad Genetics

Ruofei Du
No relationship to disclose

Ji-Hyun Lee
No relationship to disclose

Amanda Gammon
Honoraria: InVitae

Karin Butler
No relationship to disclose

Saundra S. Buys
No relationship to disclose

Antoinette M. Stroup
No relationship to disclose

Rebecca A. Campo
No relationship to disclose

Kristina G. Flores
No relationship to disclose

Jeanne S. Mandelblatt
No relationship to disclose

Marc D. Schwartz
No relationship to disclose

Acknowledgment

We thank the REACH Project participants, who made this research possible; Roger Edwards, Programmer/Analyst; and Sandra Edwards, Research Associate. In addition, we thank the study coordinators, Amy Rogers and Madison Briggs, as well as the staff and administrators at the community clinics and the Utah Cancer Registry.

Appendix

Table A1. National Comprehensive Cancer Network Risk Management Recommendations[41,43]

Risk Category	Breast and Ovarian Cancer Risk Management
Previous cancer diagnosis*	
Test status	
BRCA1/2 positive	• Follow-up of cancer as recommended by physician • Annual clinical breast examination starting at 25 years of age • Annual mammogram starting at 25 years of age • Annual breast MRI starting at 25 years of age • Consideration of prophylactic mastectomy • Recommend prophylactic salpingo-oophorectomy between 35 and 40 years of age or after childbearing is complete
Negative for familial *BRCA1/2* mutation	• Follow-up of cancer as recommended by physician • Annual clinical breast examination • Annual mammogram • Imaging with breast MRI may be considered based on personal and family history
Uninformative† or VUS	• Follow-up of cancer as recommended by physician • Annual clinical breast examination • Annual mammogram • Imaging with breast MRI may be considered based on personal and family history
No testing done	• Follow-up of cancer as recommended by physician • Annual clinical breast examination • Annual mammogram • Imaging with breast MRI may be considered based on personal and family history
Unaffected relative at risk of a familial mutation	
Test status	
BRCA1/2 positive	• Annual clinical breast examination starting at 25 years of age • Annual mammogram starting at 25 years of age • Annual breast MRI starting at 25 years of age • Consideration of prophylactic mastectomy • Recommend prophylactic salpingo-oophorectomy between 35 and 40 years of age or after childbearing is complete • Consider chemoprevention (eg, tamoxifen)‡
BRCA1/2 negative with known familial mutation§	• Clinical breast examination every 3 years until 40 years of age; then annually • Annual mammogram starting at 40 years of age
No testing done	• Annual clinical breast examination starting at 25 years of age • Annual mammogram starting at 25 years of age • Annual breast MRI starting at 25 years of age • Consideration of prophylactic mastectomy • Consideration of prophylactic salpingo-oophorectomy between 35 and 40 years of age or after childbearing is complete • Consider chemoprevention (eg, tamoxifen)‡

Abbreviations: MRI, magnetic resonance imaging; VUS, variant of uncertain significance.
*There are less specific guidelines for patients with cancer. Recommendations depend on the individual's cancer history and are made in consultation with their oncologist. For example, patients with cancer may take estrogen inhibitors (ie, tamoxifen) as treatment rather than chemoprevention, as is the case for unaffected relatives.
†Test result uninformative is defined as no pathogenic mutation identified in the family, and the cause of the cancer risk remains unknown.
‡The survey assessed chemoprevention only in the at-risk family member group because these drugs are often used for treatment in people with a cancer diagnosis.
§For those in this category, it is important to consider cancer history from the other side of the family.

Table A2. Noninferiority of Telephone to In Person Counseling for Psychosocial, Quality-of-Life, and Informed Decision–Making Outcomes by Intervention Arm and Previous Cancer Diagnosis Versus At-Risk Relative

	Cancer Case					Relative				
	Telephone		In Person		Difference, (TEL - IP)	Telephone		In Person		Difference, (TEL - IP)
Outcome	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
Anxiety*	395	−0.05 (−0.28 to 0.19)	370	−0.08 (−0.34 to 0.22)	0.04 (−0.86 to 0.36)	8	1.63 (0.13 to 4)	12	−0.25 (−0.89 to 0.57)	1.88 (−0.66 to 3.89)
Cancer-specific distress*	387	−3.85 (−5.03 to −2.78)	357	−4.32 (−5.54 to −3.06)	0.47 (−2.67 to 1.83)	8	−0.13 (−3.63 to 6.4)	12	−7.67 (−12.32 to −1.55)	7.54 (−2 to 14.68)
Quality of life: physical health*	390	−0.45 (−1.2 to 0.2)	368	0.01 (−0.65 to 0.66)	−0.46 (−1.34 to 1.04)	7	2.96 (0.74 to 4.44)	11	−0.31 (−3.28 to 2.68)	3.27 (−0.18 to 9.55)
Quality of life: mental health*	390	−0.78 (−1.58 to 0.08)	368	−1.03 (−1.91 to −0.2)	0.26 (−0.725 to 2.19)	7	−1.36 (−5.76 to 3.64)	11	−2.95 (−7.41 to −0.45)	1.59 (−3.02 to 11.48)
Decisional conflict	371	27.02 (25.38 to 28.62)	343	27.15 (25.55 to 28.7)	−0.13 (−4.09 to 1.75)	8	14.84 (8.75 to 19.53)	12	19.11 (9.24 to 34.38)	−4.26 (−41.96 to 5.44)
Decisional regret	369	21.27 (19.39 to 23.02)	342	22 (20.06 to 23.77)	−0.72 (−4.48 to 1.375)	8	11.88 (4 to 16.11)	12	3.75 (0.22 to 8.75)	8.13 (−7.92 to 12.98)
Perceived personal control	397	1.52 (1.48 to 1.55)	368	1.52 (1.49 to 1.56)	−0.01 (−0.05 to 0.08)	8	1.81 (1.73 to 1.93)	13	1.79 (1.63 to 1.95)	0.01 (−0.15 to 0.41)

Abbreviations: IP, in person; TEL, telephone.
*Values indicate change from baseline.

Table A3. Noninferiority of Telephone to In-Person Counseling for Psychosocial, Quality-of-Life, and Informed Decision–Making Outcomes by Intervention Arm and Test Result Status

	Negative					Positive					Uninformative					Nontester				
	Telephone		In Person		Difference (TEL - IP)	Telephone		In Person		Difference (TEL - IP)	Telephone		In Person		Difference (TEL - IP)	Telephone		In Person		Difference (TEL - IP)
	n	Mean, 95% CI	n	Mean, 95% CI	Mean, 95% CI	n	Mean, 95% CI	n	Mean, 95% CI	Mean, 95% CI	n	Mean, 95% CI	n	Mean, 95% CI	Mean, 95% CI	n	Mean, 95% CI	n	Mean, 95% CI	Mean, 95% CI
Anxiety*	4	0.75 (−1.0 to 1.33)	9	−0.33 (−0.92 to 0.4)	1.08 (−1.67 to 1.93)	12	0.33 (−0.87 to 1.35)	12	−0.25 (−2 to 1.82)	0.58 (-3.64 to 2.33)	89	0.11 (−0.32 to 0.52)	109	−0.48 (−0.95 to −0.02)	0.59 (−0.43 to 1.11)	291	−0.12 (−0.41 to 0.18)	247	0.08 (−0.27 to 0.41)	−0.19 (−0.93 to 0.18)
Cancer- specific distress*	4	−3.0 (−7.0 to −1.67)	9	−6.89 (−12.8 to 4.78)	3.89 (−18.67 to 9.56)	11	−2.09 (−9.01 to 5.54)	12	−2.25 (−8 to 1.79)	0.16 (−15.61 to 7.71)	87	−5.23 (−7.27 to −3.36)	103	−4.55 (−6.8 to −2.46)	−0.68 (−5.68 to 1.78)	286	−3.59 (−5.0 to −2.31)	240	−4.63 (−6.15 to −3.14)	1.04 (−2.17 to 2.76)
Quality of life- physical health*	4	3.48 (−0.3 to 4.73)	8	−0.76 (−3.45 to 1.43)	4.24 (−0.6 to 10.35)	11	2.19 (−1.49 to 5.76)	12	−0.86 (−4.57 to 2.32)	3.06 (−1.0 to 11.32)	89	−1.21 (−2.78 to 0.39)	109	−0.51 (−1.94 to 0.93)	−0.7 (−2.43 to 2.42)	286	−0.24 (−1.03 to 0.53)	245	0.27 (−0.51 to 1.04)	−0.51 (−1.45 to 1.47)
Quality of life- mental health*	4	−3.49 (−6.74 to 6.25)	8	−1.65 (−5.76 to 0.55)	−1.84 (−6.29 to 14.41)	11	−2.74 (−9.87 to 3.2)	12	−0.07 (−1.72 to 1.9)	−2.68 (−8.36 to 7.75)	89	0.19 (−1.43 to 1.72)	109	−0.09 (−1.68 to 1.59)	0.28 (−1.75 to 3.78)	286	−0.89 (−1.84 to 0.13)	245	−1.45 (−2.5 to −0.49)	0.56 (−0.56 to 2.87)
Decisional conflict	5	13.44 (0 to 21.88)	8	22.27 (6.88 to 43.75)	−8.83 (−45.38 to 5.76)	12	23.44 (15.0 to 31.1)	13	21.96 (15.27 to 31.67)	1.47 (−21.33 to 9.88)	86	16.82 (13.64 to 20.46)	99	22.74 (19.96 to 25.75)	−5.91 (−13.2 to −2.02)	270	30.37 (28.5 to 32.26)	231	29.16 (27.37 to 30.94)	1.21 (−2.49 to 3.25)
Decisional regret	5	9 (0 to 15.0)	8	7.5 (1.43 to 15)	1.5 (−17.86 to 8.97)	12	20 (12.21 to 28.33)	13	8.08 (2.26 to 17.5)	11.92 (−6.26 to 20.81)	86	9.53 (6.91 to 12.5)	99	13.59 (10.8 to 16.77)	−4.05 (−9.66 to −0.38)	268	25.2 (23.09 to 27.33)	230	25.95 (23.83 to 28.25)	−0.74 (−5.65 to 1.71)
Perceived personal control	5	1.73 (1.44 to 2.0)	9	1.8 (1.62 to 1.99)	−0.07 (−0.34 to 0.32)	12	1.55 (1.28 to 1.77)	13	1.73 (1.46 to 1.9)	−0.18 (−0.46 to 0.48)	90	1.63 (1.55 to 1.7)	109	1.61 (1.54 to 1.67)	0.02 (−0.06 to 0.16)	291	1.48 (1.44 to 1.53)	245	1.48 (1.43 to 1.53)	0.0 (−0.05 to 0.1)

Abbreviations: IP, in person; TEL, telephone.
*Values indicate change from baseline.