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Results From the Genetic Information and Family Testing Study: A Cluster-Randomized Trial

Steven J. Katz, MD, MPH[1,2]; Timothy P. Hofer, MD[1]; Paul Abrahamse, MA[1]; Rebecca R. Courser, MPH[1]; Rachel Hodan, MS[3]; Rachel S. Tocco, MA[4]; Sonia Rios-Ventura, BA[5]; Kevin C. Ward, PhD[6]; Ann S. Hamilton, PhD[7]; Melissa K. Frey, MD, MS[8]; Lawrence C. An, MD[1]; and Allison W. Kurian, MD, MSc[5,9]

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ABSTRACT

PURPOSE Cascade genetic testing in families with hereditary cancer syndromes is an important strategy to reduce the burden of cancer, but testing of relatives is low. Direct engagement of relatives through cancer survivors is a promising approach to bridge this gap.

METHODS We conducted a population-based cluster-randomized clinical trial (Genetic Information and Family Testing [GIFT]) of an online, direct-to-family, cancer genetic education and communication tool including the offer of home testing to adult relatives of cancer survivors diagnosed in 2018-2019 who carried a pathogenic variant. We selected patients through SEER and surveyed them for eligibility followed by a trial invitation. Two features were randomized: assistance from a human navigator (yes, no) and testing cost (free *v* $50). We hypothesized that the fraction of relatives tested in a family (primary outcome) would be higher with a navigator and free testing.

RESULTS Four thousand three hundred patients were surveyed and 2,285 responded (53.1%); 2,006 eligible respondents were invited (87.8%) and 414 enrolled (20.6%). Enrolled patients reported a total of 4,946 first- and second-degree relatives (mean, 12.3; standard deviation [SD], 8.6); they invited 948 relatives (19.2%) and 303 enrolled (32.0%). Most enrolled relatives ordered testing (267, 91.3%); more than double were tested in the free versus $50 arm (odds ratio [OR], 2.5 [1.6-3.9]), but the baseline fraction tested was low at 0.03 and thus the absolute increase was modest (0.04 [95% CI, 0.02 to 0.05]). We did not find evidence for increased testing in the navigation arm (OR, 1.3 [0.8-2.1]).

CONCLUSION GIFT is a promising blueprint for online cascade genetic education and testing. Results suggest that a low-cost, population-level intervention could be deployed without a human navigator. Additional intervention strategies are needed to increase the modest invitation and testing uptake observed in this study.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Providing cascade genetic risk education and testing to families with inherited cancer susceptibility (hereditary cancer syndromes [HCS]) is a growing challenge as more patients with cancer receive germline testing.[1-7] A pathogenic variant (PV) in a cancer susceptibility gene detected in a patient after cancer diagnosis has important implications for families because at-risk relatives (ARR) can be offered genetic education and testing.[8,9] Genetic cancer risk assessment is complex, as there are over 40 cancer genes with clinically actionable PVs. But the associated cancer risks of PVs in these genes vary, as do the recommendations made by guideline organizations for early detection and prevention strategies.[10-13]

Families with HCS have limited access to genetic risk education and testing: oncologists concentrate on treatment of the patient with diagnosed cancer, while genetic counselors face increasing demands from the rising numbers of patients undergoing genetic testing, with little likelihood of a near-term increase in the supply of counselors. Insurance barriers and Health Insurance Portability and Accountability Act regulations limit clinician engagement with relatives in these families.[14] As a result, most ARRs fail to receive meaningful genetic risk education and testing.[15]

Direct engagement of individuals with HCS is a promising approach to bridge the genetic evaluation gap within their families.[16-18] We conducted a population-based, two-by-two, cluster-randomized clinical trial to implement and

CONTEXT

Key Objective

Can an online genetic education and communication tool offered to cancer survivors who carry a pathogenic variant reduce the gap in cascade genetic testing in families with hereditary cancer susceptibility?

Knowledge Generated

One fifth of eligible patients enrolled in the trial; they invited nearly 20% of their relatives to the trial; and a third of invited relatives enrolled. More than twice as many relatives were tested in families offered free versus $50 home genetic testing, but there was no increased testing in families offered the addition of a human navigator.

Relevance *(S.B. Wheeler)*

This study illustrates how patients identified through population-based ascertainment respond to interventions to improve cascade testing rather than relying on recruitment through large tertiary academic centers. Although the overall response was somewhat low, results suggest that offering free cascade testing in families is beneficial and that human navigation does not add additional value.*

*Relevance section written by *JCO* Associate Editor Stephanie B. Wheeler, PhD, MPH.

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evaluate an online, direct-to-family, personalized education and communication tool, including the offer of low-cost home genetic testing, to close the gap in genetic risk evaluation and inform prevention and early detection strategies for relatives of cancer patients with HCS. Two features of the intervention were randomized at the family cluster and evaluated to determine the best approach for future scalability of the online Genetic Information and Family Testing (GIFT) platform: assistance from a lay human navigator (yes, no) and genetic test cost (free *v* $50). We hypothesized that increased navigation support and free testing would (1) increase the proportion of first- and second-degree relatives reported by patients on baseline survey who complete genetic testing through the study platform (primary outcome); (2) increase the proportion of first- and second-degree relatives reported by patients on a baseline survey who are invited by the patients to initiate genetic risk education and testing through the study platform (secondary outcome); and (3) substantially improve cancer patients' assessment of their communication with relatives about hereditary cancer and genetic risk evaluation (secondary outcome).

METHODS

Study Design and Participants

Details of the trial design and protocol have been previously published.[19] GIFT is a multilevel, two-by-two factorial, prospective cluster-randomized clinical trial (Data Supplement, Fig S1: GIFT Study Design, online only). The intervention arms included education and decision support through an Internet platform, combined with one of four levels of additional support. All intervention elements were designed to help patients feel comfortable communicating with and inviting relatives, and then subsequently to help invited relatives decide whether they would like to receive testing provided through the platform. The clusters were defined as the eligible relatives of each of the 414 enrolled index patients. We chose a cluster-level randomization because individual-level randomization of the relatives of a single index patient could lead to contamination, if relatives compared experiences with different levels of the interventions, and reduce acceptance of the intervention.

Study Patient Population and Eligibility

Patients were included if they were (1) diagnosed with any cancer at any stage in 2018-2019 and reported to the Georgia or California SEER registries; (2) found to carry a PV in one of 27 cancer susceptibility genes tested routinely by Color Health (Burlingame, CA), the testing laboratory with whom we partnered for this trial (Data Supplement, Table S1), according to the Georgia California SEER Genetic Testing Linkage Initiative data set[19]; (3) age 18 years or older; and (4) alive at the time of selection as determined through linkage with Georgia and California vital statistics data. Additional eligibility criteria, which were evaluated from patient response to the Patient Inception Cohort (PIC) survey, included confirmation of (1) receiving genetic testing for cancer risk and (2) and recalling a positive test result (PV).

Inclusion criteria for invitation of relatives were assessed via patient report: (1) first-degree or second-degree relative of a patient enrolled in the study, consistent with clinical guidelines for families with HCS[7,10]; (2) age 18 years or older; (3) alive at the time of study invitation; and (4) relative lived in the United States or Canada (countries in which Color Health genetic testing is available). All relatives reported by the patient as eligible were included in the protocol-

specified analyses under an intention-to-treat approach, even if later found after randomization to be ineligible for testing. After patient randomization, relatives who responded to an invitation were screened before they were offered testing to confirm that they (1) had not received germline genetic testing ordered by a doctor or a genetic counselor within the previous 5 years; (2) were age 18 or older; (3) were a first-degree or second-degree relative to the patient; and (4) were a resident of the United States or Canada.

Patient Trial Enrollment and Family Cluster Randomization

Details of the trial enrollment and subject randomization have been published[19] and are summarized in Figure 1 and Figure 2. The investigators obtained informed consent from each participant, and research was performed after approval by local human investigations committees and the Department of Health and Human Services.

Intervention

We studied the effects of two intervention features that were randomized in a factorial design, producing four arms: the first feature was the level of personalized genetic education and testing decision support. For this feature, the control arm was a web-based, technology-assisted patient and family member education and communication tool, and the intervention arm was the tool plus direct assistance from a human navigator. The second feature of the intervention was the cost of the genetic test offered to the relatives in a family. The control arm was $50, and free testing was the intervention. The intervention components were directed at both the index patient (cluster level) and relative (individual level). Further details about the components of the two interventions are described in the Data Supplement (Appendix A1).

Outcomes

Family Genetic Testing

The primary outcome was whether an eligible relative was tested or not, on the basis of a final report from Color Health 6 months after the final relative enrolled in the trial.

Relative Invitation

One secondary outcome was whether or not a relative was invited to visit the GIFT educational website platform. A relative was considered invited if the index patient used the website to initiate an invitation to that relative. All eligible relatives, as reported by the index patient on the baseline PIC survey, were included for both testing and invitation outcomes in an intention-to-treat analysis, regardless of whether they were invited to the trial or found to have already been tested after they visited the website.

Assessment of Family Communication Scale

A second secondary outcome was a 20-item scale that measured patient comfort with communication with relatives about genetic testing (see the Data Supplement, Table S2 and Fig S2, for scale items and attributes). The outcome was continuous, and a higher score, controlling for the baseline, indicated greater improvement in the patient's assessment of their communication with relatives. The scale was standardized to have a mean of 0 and standard deviation (SD) of 1 for the analysis. This outcome was assessed only in respondents of the patient follow-up survey.

Analysis Plan

The analysis plan is unchanged from that described in our protocol paper,[19] and documented on clinicaltrials.gov (ClinicalTrials.gov identifier: NCT05552664). The testing and invitation outcomes were analyzed at the individual relative level with a multilevel logistic regression model that accounts for the cluster randomization into the trial arms. As prespecified, no interaction term was included, given the expected absence of any synergy between the two interventions. An online supplement includes a sensitivity analysis with the interactions included.[20] These outcomes are reported as predicted probabilities of testing (or invitation) conditional on the other intervention being set to that of the control group. Several prespecified covariates were included for design and efficiency reasons, including family size, relative sex as reported by the index patient, and the baseline, patient-reported assessment-of-communication-with-family scale score. We then estimated the marginal main effect of each intervention by averaging over the distribution of the covariates and random effects included in each model, conditional on the other intervention being at the control level. This strategy standardizes the intervention effect to a large and representative population, with the distribution of covariates found in the combined SEER catchment areas of Georgia and California, who were willing to enroll in a program to increase informed family participation in genetic testing.

For secondary aim 2 (Assessment of Family Communication Scale at 6 months after enrollment), we used a linear regression at the level of the index patient to estimate the main effects of cost reduction and navigator help. Each index patient's baseline communication assessment score and cluster size were included as covariates. The main effects of each intervention are quantified by the marginal effect of each intervention variable, averaging across the included covariates and family random effects, and conditional on the other intervention being set to the control group. Details of the sample size calculations are described in the protocol paper.[19] All analyses, including the results presented here and in the Data Supplement, and all others done as part of the preparation of this paper, are presented along with the code for the analyses and all tables and figures in an online supplement at a public GitHub site.[21]

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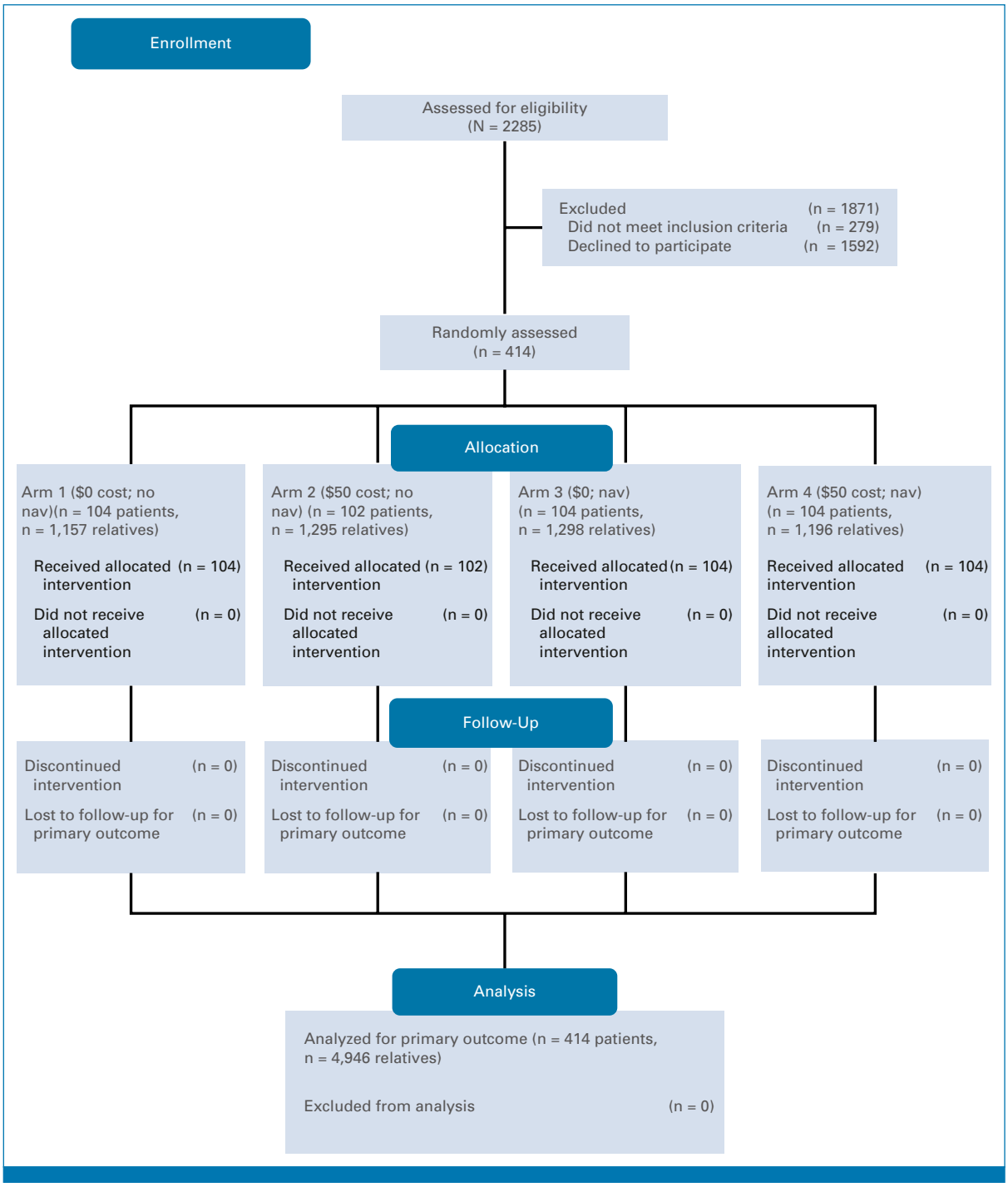

FIG 1. CONSORT diagram of the progress through the phases of the trial of four groups.

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RESULTS

A total of 4,300 patients were surveyed and 2,285 responded (53.2%); 2,006 respondents were eligible and invited to GIFT (87.8%); and 414 of the invited patients enrolled (20.6%). The median number of days from cancer diagnosis to laboratory test accession date was 35 (range, −585 to 1,953); and from diagnosis to patient enrollment date was 1,527 (range, 568-2,162). The Data Supplement (Table S3) shows clinical and sociodemographic characteristics of the enrolled patients: 82% linked to a hereditary breast/ovarian cancer gene PV and 17% linked to a Lynch syndrome gene PV; 65% had breast cancer; and 89% were female. Enrolled patients reported on the baseline cohort survey that they shared test results with 88% of their first-degree relatives and 42% of their second-degree relatives.

Enrolled patients reported a total of 4,946 first- and second-degree eligible relatives (mean 12.3, SD, 8.6), and 948 relatives were invited by patients to GIFT (19.2%). There was

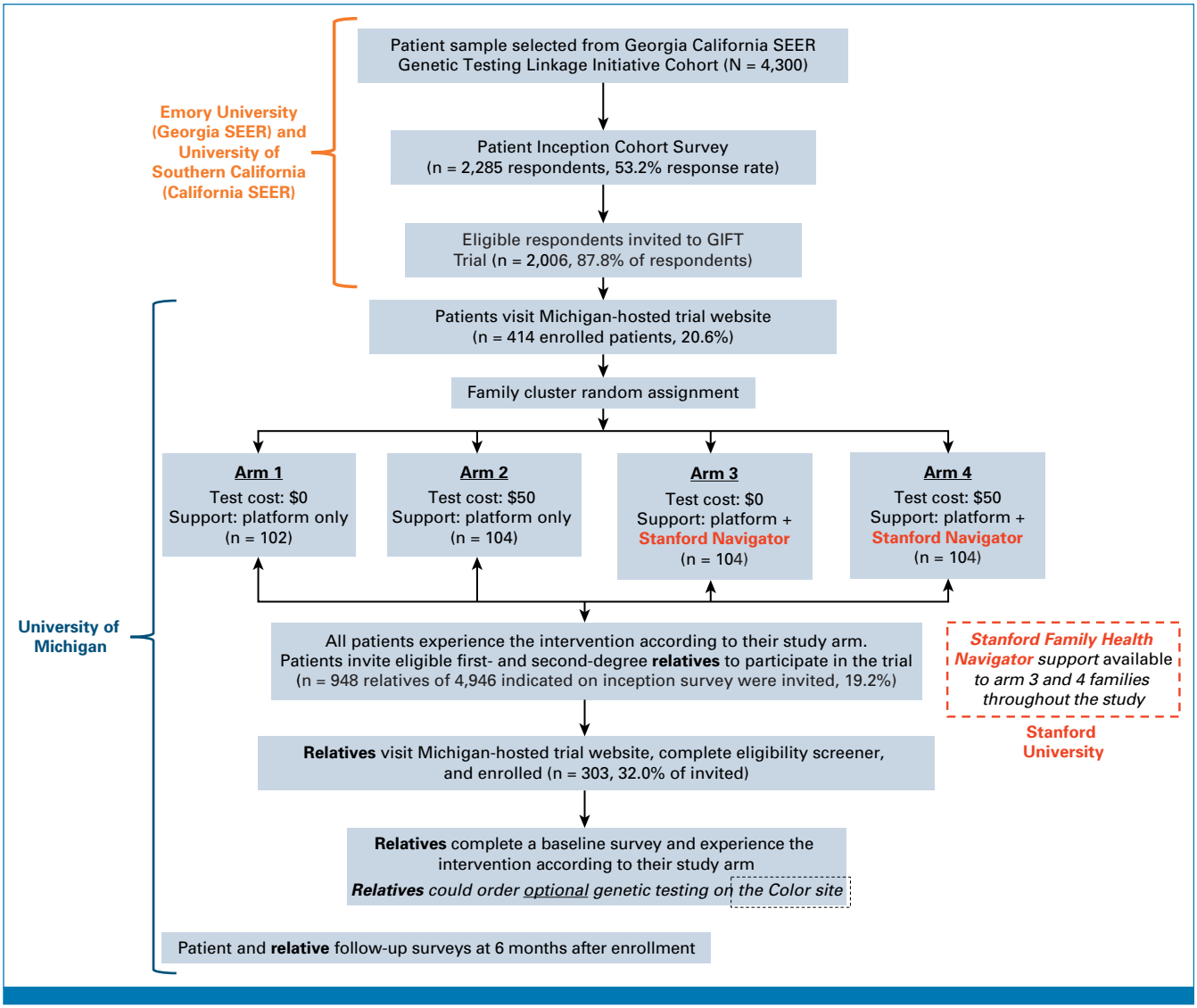

FIG 2. Summary of the GIFT trial protocol and study flow. Normal text indicates study flow related to patients. Bolded text indicates study flow related to relatives. The figure also shows the project sites responsible for the activities described across the study flow. GIFT, Genetic Information and Family Testing.

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wide variability in the number of relatives invited: one third of patients invited no relatives, one third invited 1-2 relatives, and one third invited three relatives or more. Three hundred and seventy-five of the 948 invited relatives initiated enrollment in GIFT (40.0%): 303 (80.8%) successfully enrolled and 72 (19.2%) completed the screener but did not meet eligibility criteria, the majority because they had undergone genetic testing in the past 5 years. Thus, 303 of the 948 invited relatives enrolled (32.0%) and most enrolled relatives ordered testing (N = 272 of 303, 89.8%). See the Data Supplement (Table S4) that describes family member invitations and enrollment by trial arm.

Primary Outcome: Cascade Testing

The protocol-specified analysis that accounts for the cluster randomization and other design features is shown in Table 1. The free versus low-cost intervention more than doubled the fraction of relatives testing, but this was from a low baseline fraction of 0.03. The results do not provide evidence supporting the effect of the navigator as an intervention to increase family cascade testing, as the difference was 0.01 and the CIs included 0.

The odds ratios (ORs) from the model used to estimate the testing fractions are shown in Figure 3. The free testing intervention had an OR of 2.5 (1.6-3.9), while the OR for the navigator intervention was 1.3 (0.8-2.1). The odds of testing were decreased by 20% for each additional five eligible relatives in a family (OR, 0.8 [0.7-0.9]) and was increased for female relatives (OR, 1.6 [1.2-2.0]). There was no evidence that testing changed on the basis of the level of comfort with family communication (from the Assessment of Family Communication Scale) reported by the index patient.

TABLE 1. Intervention and Control Group Means and Differences for Primary and Secondary Outcomes

	Primary Outcome	Secondary Outcomes	
	Relatives Tested[a]	Relatives Invited[a]	Communication[b]
Intervention Arm	Fraction [95% CI]	Fraction [95% CI]	SD [95% CI]
Group means cost			
Low-cost (no navigator)	0.03 [0.02 to 0.04]	0.20 [0.16 to 0.23]	0.12 [−0.05 to 0.29]
Free (no navigator)	0.07 [0.05 to 0.09]	0.23 [0.19 to 0.27]	−0.04 [−0.22 to 0.14]
Difference (cost)			
Free *v* low-cost	0.04 [0.02 to 0.05]	0.04 [−0.01 to 0.08]	−0.16 [−0.36 to 0.04]
Group means navigator			
No navigator (low cost)	0.03 [0.02 to 0.04]	0.20 [0.16 to 0.23]	0.12 [−0.05 to 0.29]
Navigator (low-cost)	0.04 [0.03 to 0.06]	0.17 [0.14 to 0.21]	0.05 [−0.13 to 0.22]
Difference (navigator)			
Navigator *v* none	0.01 [−0.01 to 0.02]	−0.02 [−0.06 to 0.02]	−0.07 [−0.27 to 0.13]
Number of index patients	414	414	262
Number of relatives	4,946	4,946	

NOTE. The three outcomes (one primary and two secondary) are shown in the three columns of the table. In the rows, we report the summary of the outcome for each group calculated from the results from the four study arms (the first two rows for each of the two interventions in sequence). The row labeled difference presents the contrast between the groups as the risk difference. For the continuous communication outcome, the contrast is presented as a difference in means. All effects are predicted outcomes averaged over the distribution of the prespecified covariates for each regression and also averaged over the family effects for the multilevel models. Without accounting for the cluster randomization or design features, the free arm had 182/2,455 (0.07) tested compared with the control low-cost arm, where 90/2,491 (0.04) eligible relatives were tested. The navigator arm had 155/2,494 (0.06) tested versus 117/2,452 (0.05) tested in the no navigator arm. Similarly for the invitation outcome, the free arm had 501/2,455 (0.20) invited compared with the control low-cost arm, where 447/2,491 (0.18) eligible relatives were invited. The navigator arm had 438/2,494 (0.18) invited, compared with 510/2,452 (0.21) in the control no-navigator arm.

Abbreviation: SD, standard deviation.

[a]The testing and invitation outcomes were assessed at the relative level, with relatives clustered within index patients in multilevel models. The invitation outcome was assessed 91 days after enrollment of the index patient. The test outcome was assessed 6 months after the final relative enrolled in the study.

[b]The comfort with communication outcome was assessed for index patients who responded to a survey 6 months after the intervention and results are presented in units of SDs of the scale.

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Only 13% of the family-level variation in testing fraction was explained by the intervention groups and baseline covariates. Over 40% of the remaining variation in testing (intraclass correlation, ICC = 0.41) was between families, with the predicted proportion of relatives tested varying between 0% and 30% across families, holding the baseline covariates constant.

Secondary Outcomes

Invitation to Relatives

The protocol-specified analysis in Table 1 shows in the second column the adjusted proportions tested in each arm and the difference between arms for each intervention. The point estimate described in the table for the free versus low-cost intervention comparison was 0.04, and for the navigator versus no-navigator comparison was −0.02, but for both estimates, the CIs included 0. The ORs representing the change in odds of invitation were 1.4 (0.9-2.0) for the free testing intervention and 0.80 (0.5-1.2) for the navigator intervention, while the ORs for baseline covariates were very close to those seen in the invitation model (Data Supplement, Fig S3). There was again a large amount of residual family variation (ICC = 0.47); the predicted fraction invited at the family level ranged between 0% and 90% (in the absence of either intervention and with baseline covariates at the mean).

Patients' Assessment of Communication With Relatives

Two hundred sixty two of the 414 enrolled patients completed the 6-month follow-up survey (63.3%). There was no evidence of improvement in comfort with communication with either intervention (Table 1; Data Supplement, Fig S4).

Patient Assessment of Platform and Navigator

The follow-up survey showed that patient participants generally praised the ease of using the GIFT platform and the clarity of the features: The *GIFT website was easy to use* (78.0% quite/very true); *It was easy to use the site to invite family members* (66.3% quite/very true). Patients randomly assigned to the human navigator received intensive automated reminders encouraging contact with the navigator for support: 78 of the 203 (38.4%) patients randomly assigned to the navigator arm contacted the navigator and virtually all

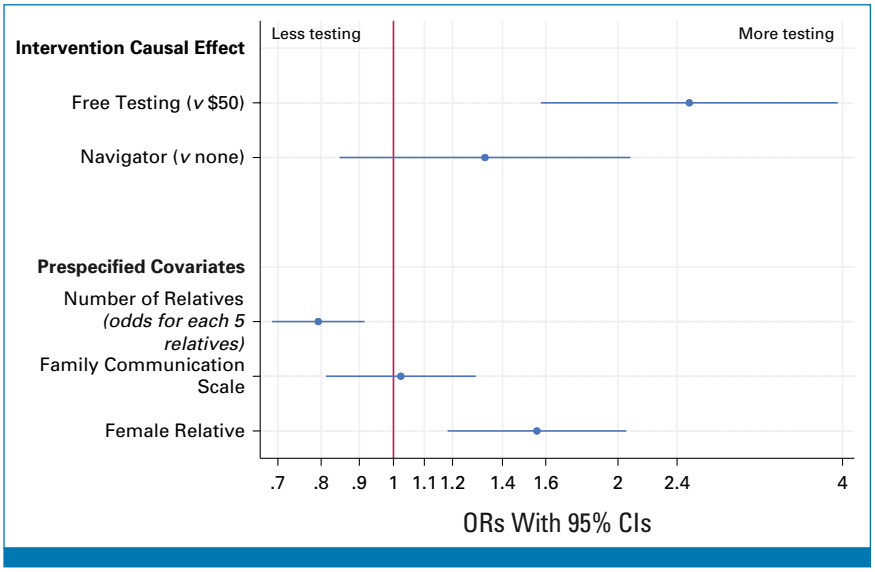

FIG 3. ORs for relative testing by intervention arm and for prespecified covariates. The *x*-axis shows the ORs for the two interventions (free *v* $50 and human navigator *v* no navigator) as well as the prespecified covariates all identified on the *y*-axis. ORs >one indicate more testing versus comparator. ORs are shown on the log scale so that reciprocal ORs are the same distance from one (eg, ORs of 0.5 and 2, which represent effects of equivalent magnitude, are shown equidistant from 1 on the log scale). Prespecified covariates were selected to improve precision of measures of the intervention effects. Number of first- and second-degree relatives was determined by information provided by patients from the baseline survey before trial invitation. The number of relatives ranged from 1 to 91 and was transformed so that 1 unit represents five relatives and is centered at the median of 14 for the analysis. The Family Communication Scale was a 20-item scale included in the GIFT baseline patient survey that measured patient comfort with communication with relatives about genetic testing (see the Data Supplement, Table S2 and Fig S2, for scale items and attributes). The outcome was continuous with a scale score range of 0.5 to 3.8 (possible range, 0-4). Higher scores indicated more favorable patient assessment of communication with their relatives. The scale was standardized to have a mean of 0 and SD of 1 for the analysis. The gender of the invited relative was determined from the family role information collected through the GIFT platform (eg, daughter, sister, mother, aunt). GIFT, Genetic Information and Family Testing; OR, odds ratio; SD, standard deviation.

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reported high ratings for the experience: *Answered my questions promptly (92.7% quite/very true)*; *Helped me understand the information from the site* (92.1% quite/very true); *Gave me helpful advice about communicating with my relatives about genetic testing for cancer risk* (90.4% quite/very).

DISCUSSION

To our knowledge, GIFT is the first cancer registry–based clinical trial to evaluate an online communication and decision-making support tool for relatives of cancer survivors with a germline PV. The platform featured education about cancer genetic risk and cancer prevention for patients and relatives, and an offer of low-cost, at-home genetic testing to relatives.

Although we found that the fraction of family members tested was almost twice as high in families offered free testing versus low-cost ($50) testing, the absolute difference between groups was small. The results did not suggest that free testing can increase the invitation rate, as the CIs of both interventions included 0. An important result of GIFT is that the residual family variation in both testing and invitation dwarfed the effect sizes anticipated in our protocol: family ID explained 40% of the variation, whereas the intervention variables and baseline covariates together explained only 13%. There was wide variation in the number of relatives that index patients invited, ranging from nearly all relatives to none, and an overall modest invitation rate (19%), suggesting that cascade testing outcomes in this sample were heavily dependent on initial invitation decisions by the index patient. Further studies that evaluate family-level predictors of invitation to test will be useful to understand this finding, and to design interventions that increase the number of patients willing to invite family members.

Another important insight from GIFT is that among invited relatives who initiated enrollment, 20% did not meet criteria for our offer of genetic testing, largely because of previous

testing. The accuracy of patient knowledge of relative testing has not previously been quantified in a population sample. A consequence of inaccurate knowledge of testing in relatives on the intention-to-treat analysis is that the fraction tested and invited includes in the denominator some relatives labeled as eligible (per patient report) but not known at the time of patient recruitment and randomization to have already had previous genetic testing.

One potential reason for the lack of navigator effect is that only a minority of participants randomly assigned to that arm directly engaged the navigator, despite intensive automated reminders to do so. We speculate that this finding reflects several factors. First, one goal of human navigation was to clarify the features and processes of the GIFT trial platform, but participants generally praised the platform features and experience positively, suggesting low need to engage a human. A second, more challenging goal of navigation is to motivate patients to invite relatives; however, we did not observe this effect in GIFT. Taken together, we think that a human navigator for a virtual approach to cascade genetic testing may not be necessary.

Strengths of the GIFT Trial include a population-based, cancer registry–derived sample of patients in whom a clinically meaningful PV was detected; a high response rate on the initial survey, given the clinical context of a cancer diagnosis 4 years before survey administration; substantial success in enrollment of patients and relatives; an online intervention that was well received by patient participants; and the partnership with an experienced, Internet-based laboratory that offered at-home, multigene panel testing and post-test genetic counseling. The diversity of the enrolled patient sample reflected those who were alive and linked to a PV result at the time of initial survey; we could not engage the families of patients who had died, which remains a challenge for cascade testing initiatives.[22]

A key future consideration is the dynamics of engagement between patients and their relatives about joining an online trial that offers cancer genetic education and testing. We need to learn more about family variation in inviting relatives to inform strategies to increase cascade testing. The modest rate of invitations to relatives and enrollment on GIFT, which yielded a small increase in overall family testing, is a critically important target for future interventions. Modest uptake may have reflected patient uncertainty about relatives' interest in testing some years after patients initially shared test results. Engaging patients earlier after cancer diagnosis might increase family invitation to interventions such as the one tested here.

We estimate that over 250,000 patients diagnosed with cancer this year in the United States will undergo germline testing, and this number will continue to grow. Nearly 15% (N = 38,000) per year will have a clinically relevant PV, with important implications for their relatives. Thus, over the next decade, many thousands of patients with cancer will be confronted with the need to share positive genetic test results with relatives, to inform decisions about cascade testing, cancer prevention, and early detection. The survivorship period is an opportune time for cascade testing interventions because (1) germline testing frequently occurs months after the cancer diagnosis[6]; (2) gaps persist in cascade testing of relatives, despite frequent patient communication with relatives about test results; (3) survivors receive little clinician support to directly engage their families; and (4) survivors express strong interest in direct support of their relatives to facilitate education and opportunities for at-home testing.[23]

GIFT offers a promising blueprint for delivery of an online platform to increase cascade genetic education and testing. Additional research is planned to develop strategies that increase intervention uptake in patients and relatives; to incorporate additional features that facilitate personalized family communication; and to offer these tools to a broad array of clinicians and health care systems.

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AFFILIATIONS

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[2]Department of Health Management and Policy, School of Public Health and Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[3]Cancer Genetics, Stanford Health Care, Stanford, CA
[4]Department of Psychiatry, University of Michigan, Ann Arbor, MI
[5]Department of Medicine, Stanford University, Stanford, CA
[6]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA
[7]Department of Preventive Medicine, University of Southern California, Los Angeles, CA
[8]Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY
[9]Department of Epidemiology and Population Health, Stanford University, Stanford, CA

CORRESPONDING AUTHOR

Steven J. Katz, MD, MPH; e-mail: skatz@umich.edu.

EQUAL CONTRIBUTION

S.J.K., T.P.H., L.C.A., and A.W.K. contributed equally to this work.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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Financial support: Steven J. Katz, Lawrence C. An, Allison W. Kurian
Administrative support: Steven J. Katz, Rebecca R. Courser
Provision of study materials or patients: Steven J. Katz, Kevin C. Ward, Ann S. Hamilton
Collection and assembly of data: Steven J. Katz, Paul Abrahamse, Rebecca R. Courser, Sonia Rios-Ventura, Kevin C. Ward, Ann S. Hamilton, Melissa K. Frey, Lawrence C. An
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Results From the Genetic Information and Family Testing Study: A Cluster-Randomized Trial

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Melissa K. Frey
Employment: WndHLTH
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Allison W. Kurian
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