Genetic Risk Assessment for Cancer Education and Empowerment Project (GRACE)

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GRACE Statistical Analysis Plan

1. Le Compte CG, Lu SE, Ani J, McDougall J, Walters ST, Toppmeyer D, Boyce TW, Stroup A, Paddock L, Grumet S, Lin Y, Heidt E, Kinney AY. Understanding cancer genetic risk assessment motivations in a remote tailored risk communication and navigation intervention randomized controlled trial. Health Psychol Behav Med. 2022 Dec 9;10(1):1190-1215. PMCID: PMC9744218.

Biostatisticians blinded to study arm assignment performed an intent-to-treat analysis using SAS v9.4, and RMediation package available in R. Summary statistics of baseline patient sociodemographic variables were compared among treatment arms using ANOVA and χ^2 tests. Pearson correlation coefficients were calculated to discern potential correlations between the selected theorized mediator variables. We calculated Cronbach's alpha to ensure internal consistency (the extent to which their respective items measured the same construct) across measures at baseline and the one-month follow-up.

Logistic regression was used to compare the percentage of CGRA intentions reported at the one-month follow-up between study arms; odds ratios and 95% confidence intervals (CIs) were calculated. We leveraged mixed model analysis to assess longitudinal between-treatment-arm and pre-to-post-differences in the scores for CGRA intentions and each theorized mediator variable. (The approach also accounted for repeated measures in our study design, as well as the 95% CIs, using linear contrasts.) We then performed mediation analysis to assess whether improvement in CGRA intentions was mediated by pre-to-post changes of the theorized meditator variables.

Due to the significant improvement in CGRA intentions for TCN compared to the other study arms, we studied the mediational relationships for CGRA intentions in TCN using the within-group analysis. We first conducted a single variable mediation analysis, in which only one theorized mediator was introduced into the model to assess its indirect effects on CGRA intentions. We followed this approach with multivariable mediation analysis, in which the theorized mediators were introduced into the model simultaneously to assess their indirect effects on the outcome. Specifically, we fitted the following models: Model 1.1: $Y_{it} = c_{0i} + c_1\text{time}_{it} + e_{1it}$; Model 1.2: $M_{it} = a_{0i} + a_1\text{time}_{it} + e_{2it}$; and Model 1.3: $Y_{it} = b_{0i} + b_1\text{time}_{it} + b_2M_{it} + e_{3it}$. In these models, Y_{ij} and M_{ij} represented CGRA intentions and mediator of subject i at time j (j = 0 for baseline and j = 1 for one-month post-intervention), respectively. We tested H_0: a_1b_2 = 0 using the confidence interval (CI) approach. If 0 was not included in 95% CI, then we rejected H_0 and established the mediation relationship. The percentage of indirect effect for significant theoretical intervention variables was calculated as $P_M = a_1b_2/c_1$.

2. Kinney AY, Walters ST, Lin Y, Lu SE, Kim A, Ani J, Heidt E, Le Compte CJG, O'Malley D, Stroup A, Paddock LE, Grumet S, Boyce TW, Toppmeyer DL, McDougall JA. Improving Uptake of Cancer Genetic Risk Assessment in a Remote Tailored Risk Communication and Navigation Intervention: Large Effect Size but Room to Grow. J Clin Oncol. 2023 May 20;41(15):2767-2778. PMCID: PMC10414736.

The primary outcome analyses were performed on an intent to-treat basis. Between-group differences in demographic and clinical variables were assessed using ANOVA and χ^2 tests. Logistic regression analysis, with CGRA uptake (yes/no) as the outcome variable, was employed to compare the treatment effect between TCN versus UC and TP as the primary analysis. Comparison between UC and TP was also performed as a secondary analysis. We also tested the effect of the interventions for those with a self-reported outcome and used both negative and multiple imputation methods to estimate CGRA uptake in

those with an unknown outcome as sensitivity analyses to determine whether the intervention effect estimates were sensitive to imputation and if the conclusions were consistent.

Multiple imputation assumed missing at random and was based on verified CGRA within 6months and demographic information; having a primary care provider; cancer site (breast *v* ovarian cancer); and number of first- and second-degree relatives with cancer, as well as the a priori interaction of the intervention with potential effect modifiers: race, ethnicity, health insurance status, literacy level, and household income. Ten imputed data sets were generated using IVEware with sequential regression, and Rubin's rule was applied to combine results using SAS Proc Mianalyze. Odds ratios, CGRA percentages, and 95% CIs were conducted using SAS v9.4.

With a final sample size of at least 212 per arm and 3% of CGRA for TP or UC, the minimum detectable OR for comparisons between TCN and TP or between TCN and UC is 1.86 with 80% power and 5% overall type I error rate (2.5% for each comparison) after multiplicity adjustment.

3. An J, Lu SE, McDougall J, Walters ST, Lin Y, Heidt E, Stroup A, Paddock L, Grumet S, Toppmeyer D, Kinney AY. Identifying Mediators of Intervention Effects Within a Randomized Controlled Trial to Motivate Cancer Genetic Risk Assessment Among Breast and Ovarian Cancer Survivors. Ann Behav Med. 2023 Oct 16;57(11):965-977. PMCID: PMC10578392.

Demographic and clinical characteristics of participants were compared among three arms using ANOVA and chi-square analysis. The mediators at baseline and 1 month were compared (within arms and between arms) using paired *t*-tests and two-sample *t*-tests; CGRA uptake at 6 months was compared using a chi-square test.

Generalized structural equation modeling (GSEM) was used for mediation analysis because CGRA uptake is a binary outcome. All 1-month cognitive and emotional mediators were controlled for baseline levels and all scores were standardized. Maximum likelihood estimation was used for estimating regression coefficients/parameters. Indirect effects were estimated, and a bootstrapping method (1,000 replications) was used to construct 95% confidence intervals.

Age, household income, education attainments, ethnicity, health insurance, urban/rural residence, cancer type, years since diagnosis, health literacy, and family history of cancer were controlled as covariates in all regressions in GSEM. We adopted negative imputation for the outcome variable, CGRA uptake – assuming no documentation meant no uptake. Sensitivity analyses with multiple imputation for missing data were conducted, based on the assumption of missing at random. Effect estimates were derived using Rubin's rule. All analyses were performed using Strata MP 17. The Monte Carlo simulation technique, was used to examine the power and estimate the minimal detectable indirect effects. Results showed that our study has at least 80% power (alpha = 0.05, two-sided) to test a minimal indirect effect of 0.37 for a single mediator and an indirect effect of 0.007-0.032 for serial mediation with two to three mediators.

4. An J, McDougall J, Lin Y, Lu SE, Walters ST, Heidt E, Stroup A, Paddock L, Grumet S, Toppmeyer D, Kinney AY. Randomized trial promoting cancer genetic risk assessment when genetic counseling cost removed: 1-year follow-up. JNCI Cancer Spectr. 2024 Feb 29;8(2):pkae018. PMCID: PMC11006111.

An intent-to-treat principle was followed in the analysis. Demographic and clinical characteristics of participants were compared across the 3 arms using ANOVA and χ^2 analysis. Logistic regression analysis was employed to compare the medically verified CGRA uptake (yes/ no) at 12months between TCN vs UC and TP; a binary intervention variable (TCN vs TP; TCN vs UC) was added to logistic models separately. Negative outcome imputation and multiple imputation were then used as sensitivity analyses to determine whether the intervention effect estimates were sensitive to imputation and if the conclusions were consistent. Negative outcome imputation assumed that CGRA did not occur if there was no documented verification. Multiple imputation was based on verified CGRA within 12months and demographic and clinical variables. Twenty-five imputed datasets were used to provide a combined estimate for missing values based on Rubin's rule, using Proc MI and Proc MIANLYZE in SAS v9.4. To estimate the cumulative probability of medically verified CGRA uptake following the intervention to 12-month follow-up, Kaplan-Meier estimates were calculated along with the 95% confidence intervals for each study arm. Participants were censored if they were lost to follow-up, or the event did not occur within the 12- month follow-up. All tests of statistical significance were 2-sided.

5. Handorf EA, McDougall JA, Heidt E, An J, Walters ST, Toppmeyer DL, Kinney AY. Cost-Effectiveness of Remote Tailored Risk Communication and Navigation for Hereditary Genetic Risk Assessment Uptake: Economic Evaluation From the Genetic Risk Assessment for Cancer Education and Empowerment Trial. JCO Oncol Pract. 2024 Dec 11;OP2400617. PMID: 39661922.

Analysis includes costs that would be incurred while implementing this intervention in a clinical practice for 212 patients (the number of patients in the TCN arm). Costs of intervention development and study-specific costs were excluded; we excluded costs of participant ascertainment and recruitment, participants' compensation, and survey administration.

The costs include the following sources: (1) training health coaches, (2) brochure printing and mailing, (3) staff costs consisting of salaries and overhead for administrative staff and health coaches, (4) participant time, and (5) downstream genetic counseling and testing and related costs. Costs were calculated in 2022 dollars from a societal perspective.

Most costs were assumed to be variable (ie, costs rise with an increased number of participants), whereas training costs were considered fixed. Our base case analysis uses the number of patients from the study to assess variable costs. In an additional scenario analysis, we increased the number of patients.