JAMA Internal Medicine | Original Investigation

Web Platform vs In-Person Genetic Counselor for Return of Carrier Results From Exome Sequencing
A Randomized Clinical Trial

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IMPORTANCE A critical bottleneck in clinical genomics is the mismatch between large volumes of results and the availability of knowledgeable professionals to return them.

OBJECTIVE To test whether a web-based platform is noninferior to a genetic counselor for educating patients about their carrier results from exome sequencing.

DESIGN, SETTING, AND PARTICIPANTS A randomized noninferiority trial conducted in a longitudinal sequencing cohort at the National Institutes of Health from February 5, 2014, to December 16, 2016, was used to compare the web-based platform with a genetic counselor. Among the 571 eligible participants, 1 to 7 heterozygous variants were identified in genes that cause a phenotype that is recessively inherited. Surveys were administered after cohort enrollment, immediately following trial education, and 1 month and 6 months later to primarily healthy postreproductive participants who expressed interest in learning their carrier results. Both intention-to-treat and per-protocol analyses were applied.

INTERVENTIONS A web-based platform that integrated education on carrier results with personal test results was designed to directly parallel disclosure education by a genetic counselor. The sessions took a mean (SD) time of 21 (10.6), and 27 (9.3) minutes, respectively.

MAIN OUTCOMES AND MEASURES The primary outcomes and noninferiority margins (δ_{NI}) were knowledge (0 to 8, $\delta_{NI} = -1$), test-specific distress (0 to 30, $\delta_{NI} = +1$), and decisional conflict (15 to 75, $\delta_{NI} = +6$).

RESULTS After 462 participants (80.9%) provided consent and were randomized, all but 3 participants (n = 459) completed surveys following education and counseling; 398 (86.1%) completed 1-month surveys and 392 (84.8%) completed 6-month surveys. Participants were predominantly well-educated, non-Hispanic white, married parents; mean (SD) age was 63 (63.1) years and 246 (53.6%) were men. The web platform was noninferior to the genetic counselor on outcomes assessed at 1 and 6 months: knowledge (mean group difference, −0.18; lower limit of 97.5% CI, −0.63; $\delta_{NI} = -1$), test-specific distress (median group difference, 0; upper limit of 97.5% CI, 0; $\delta_{NI} = +1$), and decisional conflict about choosing to learn results (mean group difference, 1.18; upper limit of 97.5% CI, 2.66; $\delta_{NI} = +6$). There were no significant differences between the genetic counselors and web-based platform detected between modes of education delivery in disclosure rates to spouses (151 vs 159; relative risk [RR], 1.04; 95% CI, 0.64-1.69; $P > .99$), children (103 vs 117; RR, 1.07; 95% CI, 0.85-1.36; $P = .59$), or siblings (91 vs 78; RR, 1.17; 95% CI, 0.94-1.46; $P = .18$).

CONCLUSIONS AND RELEVANCE This trial demonstrates noninferiority of web-based return of carrier results among postreproductive, mostly healthy adults. Replication studies among younger and more diverse populations are needed to establish generalizability. Yet return of results via a web-based platform may be sufficient for subsets of test results, reserving genetic counselors for return of results with a greater health threat.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00410241

JAMA Intern Med. 2018;178(3):338-346. doi:10.1001/jamainternmed.2017.8049
Published online January 22, 2018.

Supplemental content

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Genomic sequencing is increasingly used by medical practitioners in the care of their patients. Its use is primarily in identifying the cause of rare, undiagnosed conditions. Yet sequencing can generate multiple types of clinically relevant results, including carrier results that predict risks to future offspring, which is information that adults have interest in learning.[1] As this technology gains favor in clinical practice, it will be challenging to uphold the standard for test results to be returned in person by a knowledgeable practitioner, typically a genetic counselor or medical geneticist.[2] Not only is this face-to-face encounter impractical owing to workforce limtations, but increasing use of sequencing will migrate into mainstream medicine and primary care practitioners have significant constraints on their time to add discussions of multiple results. As such, less resource-intensive alternative delivery modes are needed for return of carrier results.[3] Such a resource would enable more primary care physicians to effectively use this emerging technology.

Genetic counseling comprises 2 related but distinct functions: the provision of genetic information[4] and psychological counseling about managing the threat of living at risk.[5] In the design of studies to assess independent effects on outcomes, the education and counseling components can be separated.[6] In a recent systematic review of randomized clinical trials (RCTs) reporting outcomes of genetic counseling for predictive genetic testing,[7] 3 studies compared education by a genetic counselor with pretest education by a web-based platform[8-12] and found equivalence or noninferiority between the intervention arms. However, to our knowledge, no published RCTs in genetic counseling have been reported that assessed differences following receipt of results.

Commercial testing companies promote the use of expanded carrier testing and have developed online platforms for returning results. To our knowledge, no reports on the evidence of the effectiveness of these interventions have been published, particularly when compared with clinical genetic counseling. Use of expanded carrier testing by practitioners is increasing and, to our knowledge, no RCT of interventions returning carrier results from exome sequencing has been reported.

We conducted a novel RCT to return results to participants in a postreproductive exome sequencing cohort. Our cohort expressed interest in learning their carrier results for themselves and the benefit of their adult children.[1] We selected the return of carrier results because they were desired and deemed low risk for adverse clinical outcomes due to participants' postreproductive status.

Our objectives were to evaluate the efficacy of a web-based platform for educating patients by assessment of noninferiority compared with a genetic counselor and determine whether observed differences between educational arms were affected by subsequent counseling. We hypothesized that the web-based platform would be noninferior to a genetic counselor in knowledge of recessive inheritance, test-specific distress, and decisional conflict about choosing to learn results.

Key Points

Question Is a web-based platform noninferior to a genetic counselor in returning carrier results from exome sequencing?

Findings In a randomized noninferiority trial of 462 adults, return of results by a web-based platform was noninferior to return by a genetic counselor. Noninferiority was assessed by the lack of significant difference in arms by 1-sided *t* tests of knowledge of recessive inheritance, test-specific distress, and decisional conflict about choosing to learn results.

Meaning Return of carrier results from exome sequencing by a web-based platform may be an acceptable, cost-effective alternative to a genetic counselor.

Methods

Eligibility Criteria

Eligible participants were primarily healthy adults from the ClinSeq cohort[13,14] (eTable 1 in Supplement 1) who (1) had completed a baseline survey, (2) were heterozygous for a variant confirmed in a Clinical Laboratory Improvement Amendments–approved laboratory in at least 1 gene causing a phenotype inherited in an autosomal-recessive pattern, and (3) had not received prior genetic test results from ClinSeq.

The National Human Genome Research Institute Institutional Review Board approved this study. Participants provided informed verbal consent; they did not receive financial compensation. CONSORT guidelines[15] and the National Society of Genetic Counselors guidelines for reporting studies were used to guide preparation of this article.[16] The study protocol is available in Supplement 2.

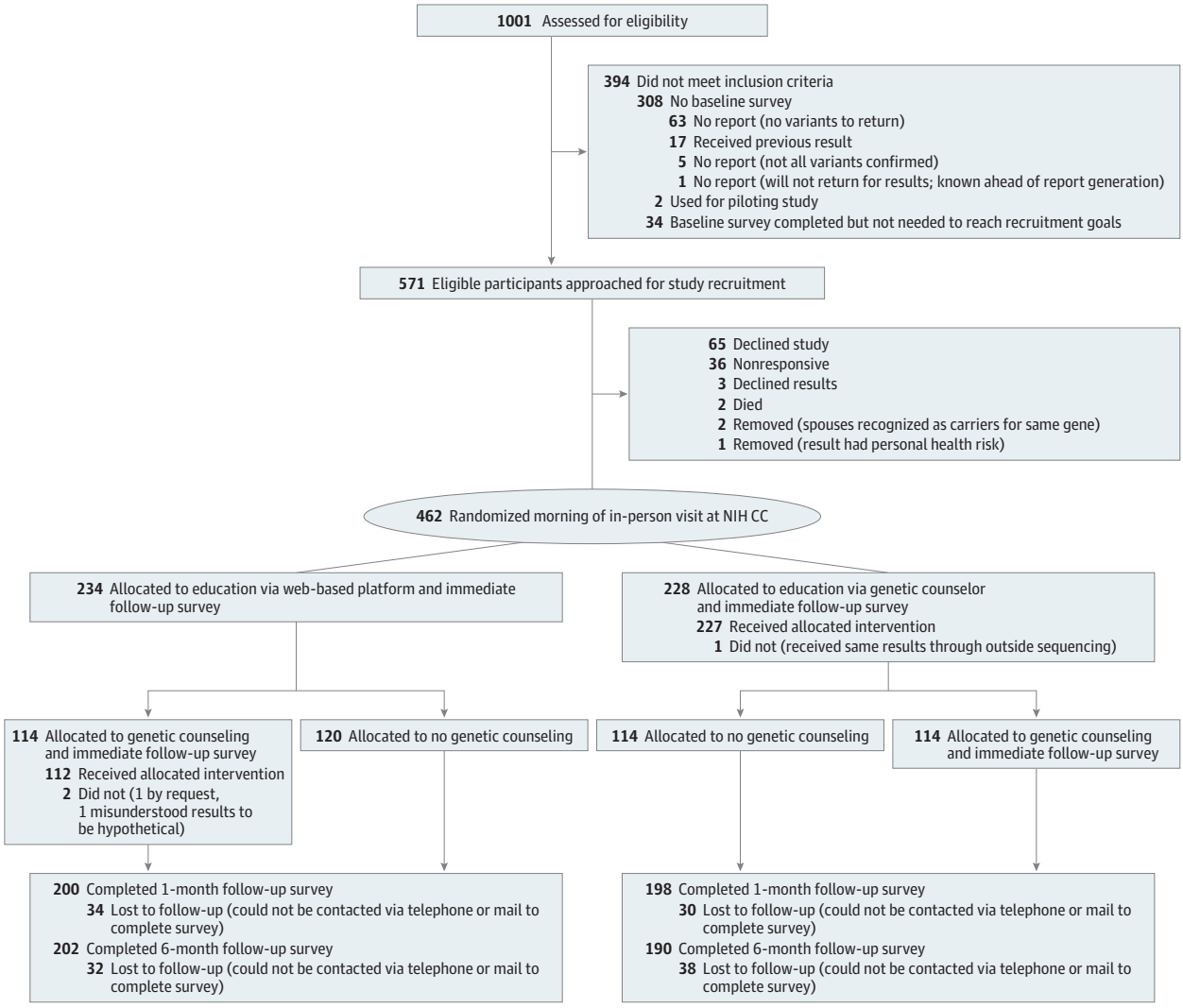
Study Design

We used a 2 × 2 between-participant factorial design. All participants were randomized to 1 of 4 study arms using an online resource (Research Randomizer, version 4.0, https://www.randomizer.org/) education by web-based platform only, education by counselor only, education by web-based platform followed by genetic counseling, and education by counselor followed by genetic counseling. Study flow is documented in **Figure 1**. Herein, we report outcomes across the educational arms because randomization to counseling had no effect on our primary outcomes as reported within. Analyses of the counseling sessions are planned for later publication.

Educational Arms

The content for the educational arms was developed using existing resources on carrier status and recessive inheritance and professional guidelines on reporting carrier results to patients.[17-21] Each education arm conveyed the same information: what it means to be a carrier, autosomal-recessive inheritance, carrier status for children and grandchildren, the participant's personal carrier results report, and testing limitations. Concepts were illustrated using identical visual aids in both arms. The individualized carrier results report included information text bubbles that defined the headings for the results

Figure 1. Participant Flow



A total of 1001 members of the ClinSeq cohort were assessed for eligibility for this trial. Ultimately, 462 individuals were randomized. NIH CC indicates National Institutes of Health Clinical Center.

in the web-based platform; the counselor explained the results in the other arm. The unique individualized risks for disease among participants' adult children and grandchildren (low in both cases but for different reasons) and manifestations of the conditions identified in a carrier state were described in both educational arms. The information (absent the names of genetic conditions) scored at a 9.2 grade level as assessed by the Flesch-Kincaid scale.[22]

The web-based platform was piloted with volunteer ClinSeq participants, and improvements were made to the description of carrier status in response to interview feedback (eAppendix in Supplement 1). Given the high level of education in the cohort and the ease of use for the pilot participants, no focus groups were conducted. If the web-based platform intervention is used in future studies of more diverse and younger populations, the reports may need to be simplified and assessed using cognitive interviewing among the target population.

The education provided by the genetic counselor (one of us, K.L.L.) was not scripted but was designed to convey the same information as the the web-based platform. The counselor deferred any counseling issues that arose in the education session.

All educational sessions were audiorecorded and transcribed. A total of 106 of 228 (46.5%) of the transcripts from the genetic counselor arm were analyzed to assess whether the major topics were addressed consistently and that ancillary topics were not introduced. This approach was key to ensuring fidelity by maintaining content similarity between study arms.

Genetic Counseling Arm

All genetic counseling sessions were conducted by the same genetic counselor (K.L.L.). Genetic counseling was distinguished from educational by considering counseling as any

participant concerns related to one's carrier results that were not information based, which were deffered if raised in the education arm.

Genetic Testing Reports

Eligible variants included those in genes associated with disorders inherited in an autosomal-recessive pattern[23,24] if there was no credible evidence of a heterozygote phenotype. Variants also (1) met quality cutoffs and a minor allele frequency cutoff of 0.15 and (2) were splice-site, stop-gain, frameshift, or missense variants previously reported in the Human Gene Mutation Database.[25] Pathogenicity assessments were generated for all variants by 1 of us (J.J.J.) and then reviewed by a panel (including several of us, K.L.L., J.J.J., and L.G.B.). A modified 6-point scale was used to classify variants as benign, likely benign, variant of uncertain significance (VOUS)-low, VOUS-high, likely pathogenic, or pathogenic based on several factors: predicted variant effect (loss of function, missense), incidence in affected individuals, frequency of variant in control populations, and functional data.[26] Variants classified as pathogenic, likely pathogenic, or VOUS-high were Clinical Laboratory Improvement Amendments (CLIA) validated and reported to participants. Participants received a CLIA report of their carrier results at the end of their visit and a letter 1 month later.

Quantitative Outcomes

Primary trial outcomes were selected from the theory of planned behavior and published RCTs: relevant knowledge, test-specific distress, and decisional conflict. Secondary outcomes included anxiety, risk worry, perceived risk, communication of results to at-risk relatives, and satisfaction. Participants completed surveys immediately after education and immediately after counseling based on randomization, 1 month later, and 6 months later. The surveys included the following scales.

Knowledge of recessive inheritance was measured at all points using 4 novel, true-false items. If both parents are carriers of a mutation associated with a recessive genetic disease, the chance that their pregnancy will be affected by that disease is 25%; if 1 parent is a carrier of a variant in a gene and the other is not, the chance that each of their children is a carrier is 25%; only 25% (1 of 4) of people's genome sequence is inherited from their mother; and a person can be a carrier for a disease even if no one else in the family has the disease. Items were responded to using a 5-point response scale coded with precedent from a validated scale[27] as 0, definitely no, probably no, and uncertain; 1, probably yes; and 2, definitely yes. Items 2 and 3 are false and so reverse scored. Summed total scores range from 0 to 8, with higher scores indicating greater knowledge (test-retest reliability: $r = 0.62$, $P < .001$).

Test-specific distress was measured at 1 and 6 months using the distress subscale of the Multidimensional Impact of Cancer Risk Assessment[28] adapted for genetic test results. Six items address the frequency with which participants have experienced a distressing emotion in the past 2 weeks on a 4-point scale: 0, never; 1, rarely; 3, sometimes; and 5, often. Summed total scores range from 0 to 30, with higher scores indicating greater test-specific distress (Cronbach α = 0.75).

Decisional conflict was measured at 1 and 6 months using the Decisional Conflict Scale,[29] which is a rating scale of 15 items. Summed total scores range from 15 to 75, with higher scores indicating greater decisional conflict about the decision to learn one's carrier results (Cronbach α = 0.94).

Disclosure rates were assessed at 1 and 6 months by asking participants whether they had told their partner or health care professional about their results. In addition, participants were asked to indicate how many biological daughters, sons, sisters, and brothers they had and how many they had told of their results. Responses were dichotomized into having told at least 1 child or sibling or not.

Risk worry was measured at baseline and at 6 months using a single, Likert-type item (How worried are you that your relatives could be affected with a genetic condition that you have passed on?) with a 7-point response scale ranging from 1, not at all worried; to 7, extremely worried (test-retest reliability: $r = 0.35$, $P < .001$).

Perceived risk was measured at baseline and at 6 months using a single item (I feel like my relatives could be affected by a genetic condition that I have passed on) with a Likert-type response scale ranging from 1, strongly disagree; to 7, strongly agree (test-retest reliability: $r = 0.42$, $P < .001$).

Anxiety was measured after education and counseling using the short-form State-Trait Anxiety Inventory,[30] which consists of 6 items on a 4-point response scale ranging from 1, not at all; to 4, very much. Summed total scores range from 6 to 24, with higher scores indicating greater anxiety (Cronbach α = 0.80).

Satisfaction was measured at 6 months using a modified version of the Genetic Counseling Satisfaction Scale,[31] which consists of 3 items (ie, I feel better about my health after getting my result[s] back, the result session was the right length of time, and the result session helped me to process the information about my result[s]), allowing for responses on a 4-point scale ranging from 1, strongly disagree; to 4, strongly agree. Summed total scores range from 3 to 12, with higher scores indicating greater satisfaction (Cronbach α = 0.86).

Power Analysis

Power calculations were based on sample sizes and SDs of the outcome measures assuming 80% power and 2-sided hypothesis tests using a $P < .05$ α-level criterion. For the immediate outcomes, the minimum detectable differences between arms were 0.61 units in knowledge and 0.79 units in anxiety. For the 6-month outcomes, the minimum detectable differences were 0.65 units in knowledge, 0.32 units in risk worry, 0.49 units in perceived risk, and 2.11 units in decisional conflict. The minimum detectable differences in proportions of dichotomous outcomes at 6 months were 32.1% in distress, 31.8% for disclosure to spouses, 37.9% for children, 43.2% for siblings, and 53.2% for health care professionals. Power at 1 month was comparable to power at 6 months.

Statistical Analysis

Differences between arms at baseline were assessed using χ^2 analysis for categorical variables and analysis of variance for continuous variables. The mean difference between educational arms (web-based platform vs counselor) and 1-sided 97.5% CI were calculated for 3 primary outcomes and 2 secondary outcomes to test for noninferiority, which was supported if the CI did not exceed the prespecified noninferiority margin (δ_{NI}): −1 in knowledge; +1 in test-specific distress, +6 in decisional conflict, +1 in risk worry, and +2 in anxiety. The δ_{NI} for test-specific distress was determined based on a published RCT[12] that found significant difference in distress (measured with the Multidimensional Impact of Cancer Risk Assessment) between those who were and were not at increased lifetime risk for type 2 diabetes; the δ_{NI} for decisional conflict was based on a margin from a previous noninferiority trial of telephone counseling[32]; the δ_{NI} for anxiety was determined based on a published RCT[33] that found no significant differences in Spielberger State-Trait Anxiety Inventory scores between graphic display and frequency format of lifetime risk for breast cancer and replicated in a more recent publication.[34] Without precedent to determine a δ_{NI} for the novel knowledge scale, the margin was set at the smallest incremental change on the scale (ie, a single point), which corresponded to approximately half an SD at baseline. For single-item measures with categorical response scales (risk worry, perceived risk), the margins were also set at the smallest incremental change. This is a conservative approach applied in noninferiority analyses where there is a lack of precedent in use of a novel scale.[32]

For the two 1-sided *t* test procedure,[35] the mean difference between educational arms (web-based platform vs counselor) and 95% CI were calculated to test for equivalence for risk perception for which provision of genetics information aims to make more accurate, but collectively not to increase or decrease. Equivalence was supported if the interval did not exceed the equivalence margin (δ_E): ±1 in perceived risk.

In secondary analyses, 2-way analysis of variance was used to assess the effect of a counseling session if significant differences were detected in primary analyses. Sensitivity analyses were conducted among those with and without children given the differential implications of receipt of results. Differences between arms in satisfaction and disclosure rates were assessed using a *t* test and the Fisher exact test, respectively. Analyses were based on available data at each point, and both intention-to-treat and per-protocol analyses were applied. For outcomes exhibiting nonnormality, robustness of the findings was verified with nonparametric tests. Parametric analyses were conducted using SPSS, Macintosh version 20.0 (IBM Corp), and nonparametric analyses were conducted using the package[36] in R with pairwise CI.

Qualitative Outcomes

Responses to the open-ended question, what, if any, information do you feel was missing from the [genetic counselor/computer] session? were independently coded by 2 of us (I.M.M., A.R.H.) using NVivo 11 (QSR International). Both investigators used the same codebook to analyze the responses by thematic analysis and reconciled most discrepancies through discussion. Intercoder reliability calculated by percent agreement was 98.8% and 99.0% in the web and counselor arms, respectively.

This study was conducted from February 5, 2014, to December 16, 2016, and ended because the 6-month response rate suggested that the target sample size would be achieved.

Results

Participants

All participants completed baseline surveys assessing psychological variables after enrollment in the ClinSeq cohort study and before enrolling in this RCT. As such, time from taking the baseline survey to participation in the RCT varied: time elapsed ranged from 4 months to 4 years (mean [SD], 1.9 [0.7] years). This duration was approximately normally distributed and not significantly associated with any covariates and thus was not contolled for in the analyses. Barring the 3 individuals excluded after randomization, all participants completed in-trial surveys. A total of 398 (86.1%) participants returned 1-month surveys and 392 (84.8%) returned 6-month surveys; nonresponders did not differ significantly from the 462 participants in any demographic variables. All 462 of 571 eligible participants (80.9%) provided informed verbal consent to participate in the RCT.

Overall, this sample was predominantly married, well-educated, postreproductive, and non-Hispanic white; these characteristics were not significantly different from the full ClinSeq cohort.[13] Mean (SD) age of the participants was 63 (63.1) years; other demographic and session characteristics are reported in **Table 1**. The randomization was effective as there were no significant differences in any variables at baseline.

Fidelity to the Intervention

Fidelity to the counselor arm ranged from 83% to 100% (mean [SD], 95% [5.6%]) across the 8 central topics and their subdomains (eTable 2 in Supplement 1). As such, the content of the information conveyed in both educational arms was highly consistent with the exception of information tailored to the patient's personal variant results, as designed.

Quantitative Outcomes

Means (SDs) of study variables by education arm are given in **Table 2**. Bivariate analyses resulted in no significant differences between educational arms in any of these variables at baseline. The web-based platform was noninferior to the genetic counselor in terms of knowledge assessed immediately after education and all primary outcomes assessed 1 month later: knowledge, test-specific distress, and decisional conflict. The main analysis at 6 months yielded consistent results. There were no significant differences at 6 months between educational arms in knowledge (mean group difference, −0.18; lower limit of 97.5% CI, −0.63; δ_{NI} = −1), test-specific distress (median group difference, 0; upper limit of 97.5% CI, 0; δ_{NI} = +1), or decisional conflict (mean group difference, 1.18; upper limit of 97.5% CI, 2.66; δ_{NI} = +6). The web-based

platform was also noninferior to the genetic counselor for anxiety at the immediate follow-up and for risk worry and equivalent for perceived risk at 6 months. These results are represented in **Figure 2**. Because test-specific distress data exhibited a floor effect at both 1- and 6-month follow-ups, violating normality assumptions for parametric tests, differences between educational arms were assessed with nonparametric tests. No significant differences were detected at either time point nor did the nonparametric CIs exceed the noninferiority margin (δ_{NI} = +1), which supports the hypothesis of noninferiority.

Based on an observed statistically significant difference between the educational arms (although not clinically significant by our margin for anxiety, δ_{NI} = +2), analysis of variance testing was used to evaluate differences in anxiety immediately following counseling or no counseling, based on randomization (eFigure in Supplement 1). The interaction effect was significant ($F_{1,448}$ = 6.94, P < .009), suggesting that the difference in anxiety between educational arms resulted from whether counseling followed education.

All analyses were run separately for those with and without children and the results were consistent for each of the outcomes except decisional conflict at 6 months: the mean difference between educational arms was 2.43 (95% CI, 0.77 to 4.09) among those with at least 1 child, whereas the mean difference was −1.79 (95% CI, −5.69 to 2.12) among those with no children. Thus, parents reported statistically significantly greater decisional conflict when educated by the web-based platform (not exceeding δ_{NI} = +6)—an effect not observed among participants without children.

Satisfaction was high overall (mean [SD], 9.86 [2.12]) but significantly lower in the web-based platform arm at 6 months: the mean difference between educational arms was 1.11 (95% CI, 0.71-1.52; P < .001). As reported in **Table 3**, there were no significant differences observed between educational arms in rate of disclosure to spouses, children, siblings, or health care professionals at 1 or 6 months; however, the power to detect differences was low.

Qualitative Outcomes

Immediately after the educational intervention, 174 of 225 (77.3%) participants in the counselor arm and 96 of 193 (49.7%) in the web-based platform arm answered that none or nothing was missing from the educational sessions. More participants from the web-based platform arm (31 of 193 [16.1%]) than from the counselor arm (5 of 225 [2.2%]) requested additional information specific to their results, such as disease treatment options, risk of disease, and testing options for family members, as well as the frequency and prevalence of their variant in the general population.

Table 1. Participant Demographics and Clinical Characteristics

Characteristic	Genetic Counselor (n = 227)	Web Platform (n = 232)
Dichotomous Classification, No. (%)		
Sex		
Male	127 (55.9)	119 (51.3)
Female	100 (44.1)	113 (48.7)
Marital status		
Not in a marriage-like partnership	49 (22.2)	45 (20.3)
In a marriage-like partnership	172 (77.8)	177 (79.7)
Annual household income, $		
≤100 000	52 (24.0)	53 (23.9)
>100 000	165 (76.0)	169 (76.1)
Education		
<Postgraduate degree	77 (34.8)	90 (40.2)
Postgraduate degree	144 (65.2)	134 (59.8)
Race		
White	215 (94.7)	211 (91.3)
Nonwhite	12 (5.3)	20 (8.7)
Ethnicity		
Hispanic or Latino	2 (0.9)	7 (3.0)
Not Hispanic or Latino	224 (99.1)	223 (97.0)
Parental status		
0 Children	52 (24.9)	46 (22.9)
≥1 Child	157 (75.1)	155 (77.1)
Results returned		
≥1 Pathogenic	175 (77.1)	174 (75.0)
0 Pathogenic	52 (22.9)	58 (25.0)
≥1 Likely pathogenic	70 (30.8)	75 (32.3)
0 Likely pathogenic	157 (69.2)	157 (67.7)
≥1 VOUS	122 (53.7)	106 (45.7)
0 VOUS	105 (46.3)	126 (54.3)
Continuous Characteristics, Mean (SD)		
Total No. of results returned, per participant	2.4 (1.2)	2.3 (1.3)
Counseling session length, if applicable, min	11 (6.7)	11 (7.3)
Educational session length, min	27 (9.3)	21 (10.6)
Age at intervention, y	63.2 (5.4)	63.3 (5.7)

Abbreviation: VOUS, variant of uncertain significance.

Discussion

This study addresses a critical conundrum of clinical genomics: the need for less resource-intensive results delivery modes apparently conflicts with the need to maintain current standards of practice. In-person delivery of individual test results by a health care professional is the standard of care and presumed to be superior to other modes. Our data demonstrate noninferiority of a web-based platform in knowledge of recessive inheritance, test-related distress, and decisional conflict about choosing to learn results. There are important service delivery implications of these results as they suggest that carrier results can be returned to certain populations via a web-based platform that conveys relevant information with sufficient gains in knowledge and no evidence of adverse psychological well-being. These results are consistent with those of 3 other RCTs returning single genetic variant results comparing in-person with computer interventions.[8-12] With additional supporting evidence, in-person genetic counseling may be reserved for individuals receiving results that are more health threatening than carrier results.[5] Given the limits of the

Table 2. Variable Distributions

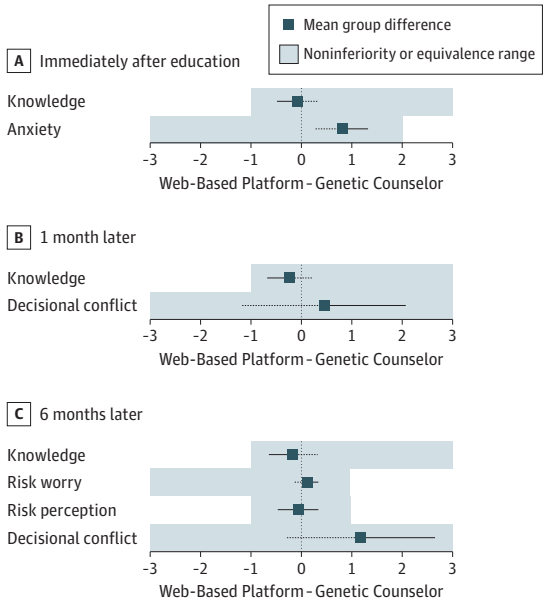
Variable (Scale Range)	Mean (SD)[a]							
	Genetic Counselor				Web Platform			
	Baseline	Immediate	1 Month	6 Months	Baseline	Immediate	1 Month	6 Months
Knowledge (0-8)	3.67 (2.12)	5.05 (2.06)	4.92 (2.20)	4.55 (2.31)	3.76 (2.31)	4.96 (2.26)	4.67 (2.23)	4.37 (2.27)
Test-specific distress (0-30)[b]	NA	NA	0.99 (2.29)	0.63 (1.79)	NA	NA	1.62 (3.47)	1.17 (2.76)
Decisional conflict (15-75)	NA	NA	20.57 (8.79)	20.40 (7.40)	NA	NA	21.00 (7.64)	21.58 (7.51)
Anxiety (6-24)	NA	7.98 (2.61)	NA	NA	NA	8.79 (2.99)	NA	NA
Risk worry (1-7)	2.52 (1.43)	NA	NA	2.15 (0.97)	2.62 (1.58)	NA	NA	2.25 (1.28)
Perceived risk (1-7)	3.90 (1.96)	NA	NA	4.35 (1.63)	3.90 (1.95)	NA	NA	4.28 (1.82)
Satisfaction (3-12)	NA	NA	NA	10.43 (1.83)	NA	NA	NA	9.32 (2.24)

Abbreviation: NA, not applicable.

[a] Cells labeled NA indicate that variable was not assessed at that time.

[b] A floor effect was observed for test-specific distress at 1 mo (median, 0; interquartile range, 1; n = 398) and 6 mo (median, 0; interquartile range, 0; n = 390).

Figure 2. Noninferiority of Trial Outcomes



Mean group differences between educational arms (web-based platform − genetic counselor) noted immediately after (A), 1 month after (B), and 6 months after (C) education with respect to 2 primary outcomes (knowledge, decisional conflict) and 3 secondary outcomes (anxiety, risk worry, risk perception). Test-specific distress is not depicted because a severe floor effect observed at 1 and 6 months rendered parametric tests inappropriate. Noninferiority was tested for outcomes shown with 1-sided 97.5% CIs, and equivalence was tested for the risk perception outcome with a 2-sided 95% CI. The gray shaded portion denotes the noninferiority (or equivalence) range defined by the prespecified margins (δ_{NI} or δ_E), which determines rejection of the null hypothesis if not exceeded. For knowledge, the possible score was 0 to 8 ($\delta_{NI} = -1$); anxiety, 6 to 24 ($\delta_{NI} = +2$); decisional conflict, 15 to 75 ($\delta_{NI} = +6$); risk worry, 1 to 7 ($\delta_{NI} = +1$); and risk perception, 1 to 7 ($\delta_E = \pm 1$).

genetics health care workforce,[3] such evidence-based alternative delivery modes will be needed. In addition, effective web-based tools for supporting sequencing would allow health care professionals to comfortably and responsibly use this new technology in their practice. This evidence can also help to inform a responsible approach to the results delivery from genome sequencing to address 1 of the challenges faced by large-scale sequencing efforts, such as the National Institutes of Health All of Us Research Program (https://www.nih.gov/research-training/allofus-research-program).

Our results demonstrate that a strong interest in learning carrier results at baseline[1] translated to downstream uptake, which differs from past research[8] and suggests that participants perceived potential value of their results for their family members. Although this sample was a well-educated group, it remains heartening that we found no indication of distress or other potential psychological harms that may arise from learning one's carrier status. Parents randomized to the web-based platform expressed greater decisional conflict about learning results, which is not unexpected in that the results pertain to risks to their grandchildren. Those randomized to the web-based platform were less satisfied with the session than were those ramdomized to a genetic counselor. In light of the noninferiority assessments for our primary outcomes and high satisfaction scores overall, the difference may not be clinically meaningful, making it difficult to justify the expense of in-person results delivery. Yet, in response to our qualitative findings, use of a web-based platform should include links to more detailed information on the specific diseases identified and risks to family members for those who desire additional information or reinforcement of the information gained.

Limitations

Our participants are of postreproductive age and early adopters of technology[14] who are capable of articulating areas of need and concern related to return of sequence information. As such, results from this study may not generalize to other populations. A replication study is planned for a more diverse, newly recruited cohort. It is also important to replicate these findings among younger adults who may use the information for reproductive decision making.

We chose carrier results for this study because they are common and numerous, but also because they have limited direct health influence on our participants. This was an important consideration for participant safety. These results

Table 3. Communication of Results

Individual	No. (%)[a]		RR Ratio[b] (95% CI)	Between-Group Differences, *P* Value[c]
	Genetic Counselor	Web Platform		
1 Month				
Spouse	154 (92.2)	160 (95.2)	0.75 (0.43-1.30)	.27
Child	83 (58.9)	88 (61.1)	0.96 (0.75-1.21)	.72
Sibling	72 (40.9)	66 (40.0)	1.02 (0.82-1.28)	.91
6 Months				
Spouse	151 (95.6)	159 (95.2)	1.04 (0.64-1.69)	>.99
Child	103 (76.9)	117 (74.1)	1.07 (0.85-1.36)	.59
Sibling	91 (57.6)	78 (49.7)	1.17 (0.94-1.46)	.18
Health care professional	57 (30.6)	54 (26.7)	1.10 (0.88-1.37)	.43

Abbreviation: RR, relative risk.

[a] Percentages refer to proportions of respondents with a spouse or at least 1 child or sibling.

[b] Risk of nondisclosure for participants in the web-based platform arm compared with the genetic counselor arm.

[c] Determined using Fisher exact 2-sided hypothesis tests.

are not necessarily generalizable to exome or genome sequencing results relating to primary findings for an underlying genetic disease or to secondary findings where the current standard of disclosure by a genetics health care professional should be followed.

Conclusions

Overall, our findings suggest that use of alternative delivery modes in the return of carrier results from genome sequencing should be considered in the face of limited professional resources and the ever-present imperative to reduce health care costs. This approach could also facilitate the use of exome and genome sequencing by nongenetics health care professionals by providing a responsible approach to routine results return that does not place high demands on the ordering clinician. We speculate that similar approaches for return of other sequencing results that are nonthreatening to personal health (eg, pharmacogenetics) may be appropriate. This study provides initial evidence for the effectiveness of carrier information provision by a web-based platform in an older population, which can support the wider use of genomic testing by clinicians and allow genetics health care professionals to focus on more pressing clinical needs for which standard genetic counseling is paramount.

ARTICLE INFORMATION

Accepted for Publication: November 22, 2017.

Published Online: January 22, 2018. doi:10.1001/jamainternmed.2017.8049

Author Contributions: Dr B. Biesecker and Ms Lewis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: B. Biesecker, Johnston, L. Biesecker.
Acquisition, analysis, or interpretation of data: All authors.
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Critical revision of the manuscript for important intellectual content: B. Biesecker, Lewis, Umstead, Johnston, Turbitt, Fishler, Patton, Miller, Heidlebaugh.
Statistical analysis: B. Biesecker, Umstead.
Obtained funding: L. Biesecker.
Administrative, technical, or material support: Lewis, Johnston, Fishler, Patton, Heidlebaugh, L. Biesecker.
Study supervision: B. Biesecker, Johnston, Fishler, L. Biesecker.

Conflict of Interest Disclosures: Dr L. Biesecker serves as an uncompensated consultant to the Illumina Corp. No other conflicts were reported.

Funding/Support: Ms Lewis, Dr Johnston, Ms Fishler, Mr Patton, Mr Miller, and Dr L. Biesecker were supported by National Institutes of Health (NIH) grants HG200359 08 and HG200387 03.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Cristofer Price, PhD (Abt. Associates), and Niraj Trivedi, PhD (National Human Genome Research Institute [NHGRI]/NIH), provided statistical consultation; Julia Fekecs, BS, and Mark Fredriksen, BS, developed the web platform graphics; Gillian Hooker, PhD, ScM, provided input into study design and constructs assessed in ClinSeq; Ashlee Hulbert, BS, assisted in the laboratory; and William Fix, BS (NHGRI/NIH) assisted in piloting the study; William Klein, PhD (National Cancer Institute/NIH), and Paul Han, MD, MA, MPH (Maine Medical Center Research Institute), contributed to the constructs assessed in ClinSeq; David Ng, MD (NHGRI/NIH), served on the panel that assigned pathogenicity to variants returned; and Tyra Wolfsberg, PhD, Anh-Dao Nguyen, MS, and Mark Fredriksen, BS programmed the web platform. The contributors did not receive financial compensation outside of salary.

Disclaimer: The opinions expressed here represent those of the authors and do not necessarily represent the opinions or policies of the institutions with which they are affiliated.

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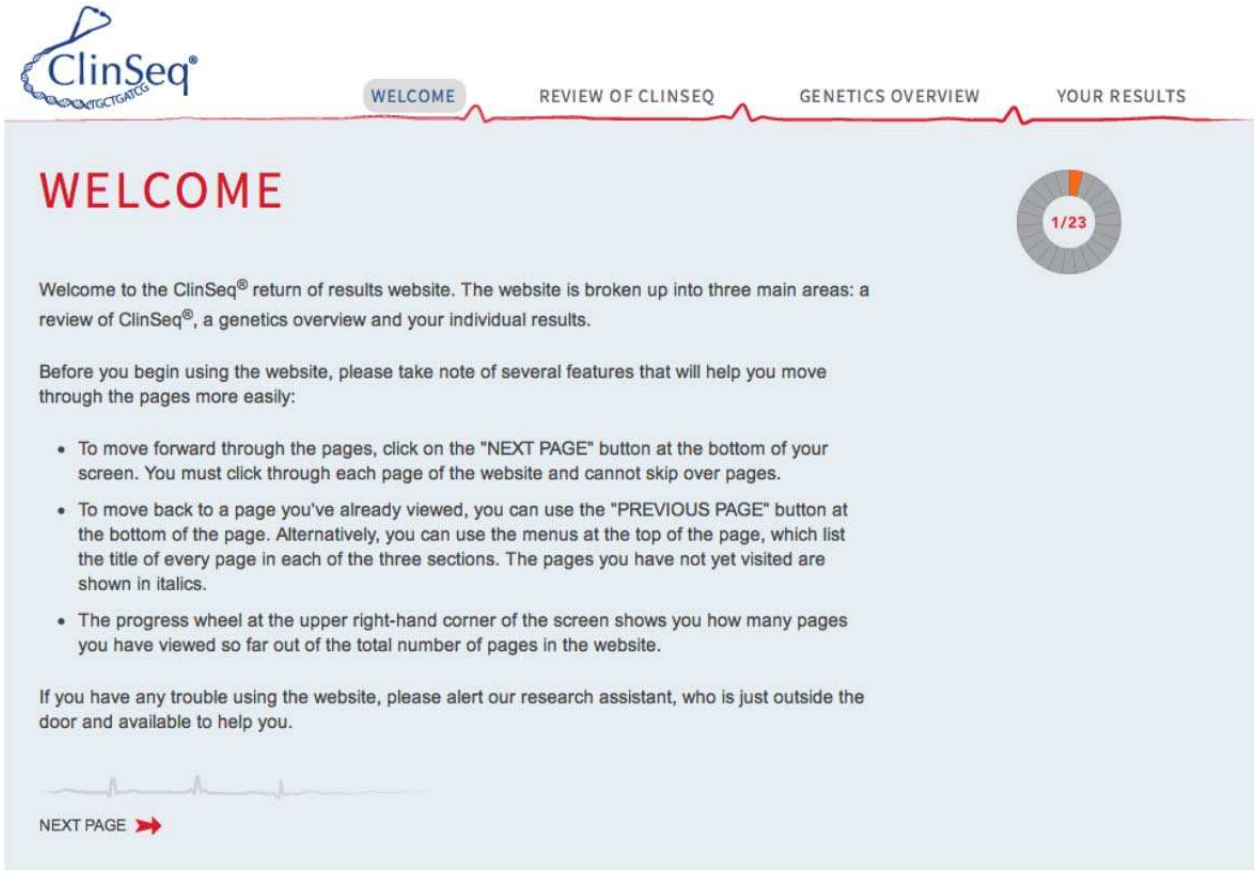
Supplementary Online Content

Biesecker BB, Lewis KL, Umstead KL, et al. Web platform vs in-person genetic counselor for return of carrier results from exome sequencing: a randomized clinical trial. *JAMA Intern Med*. Published online January 22, 2018. doi:10.1001/jamainternmed.2017.8049

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. ClinSeq



ClinSeq®

WELCOME | REVIEW OF CLINSEQ | GENETICS OVERVIEW | YOUR RESULTS

GOALS OF CLINSEQ

The overarching goal of the ClinSeq® Study is to pilot the use of a new type of genetic testing called genomic sequencing. This testing allows us to look at the majority of your genes, rather than only a limited subset that are related to a particular health condition. By doing genomic sequencing on ClinSeq® participants, we hope to accomplish three main goals:

- Develop a system for analyzing sequencing data in a research setting. This includes partnering with labs for genomic sequencing and growing our technical expertise for interpreting the data.
- Answer medical research questions about genetics, such as which genes play a role in specific health conditions or how certain genetic changes lead to health problems.
- Better understand what people think and feel about having sequencing. This includes learning more about your motivations and expectations, as well as looking at the impact of your results on family relationships, communication, healthcare and more.

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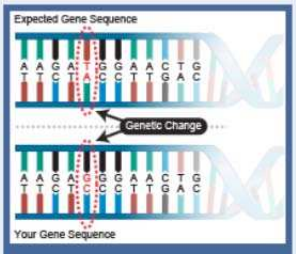
GENOMIC SEQUENCING AND INTERPRETATION

- **Genomic Sequencing:** Your genes are like a set of instructions that tell your body how to grow, develop and function. When we sequence your genes, it's as if we were reading through all of those instructions. We look at genes related to a variety of health conditions. As we read through, we look for changes, or places where your sequence differs from the reference sequence. The image to the right shows what we mean by a genetic change.
- **Interpretation:** After we find genetic changes in your sequence, we interpret them. Interpretation is a process of determining the significance of each genetic change for your health or the health of your family members. We do this using a variety of resources, including scientific papers, electronic databases and your personal and family history. We only share results with you that may affect your health or the health of your family members based on current knowledge.



This image shows what we mean when we say "genetic change". It refers to any place where your genetic sequence differs from a reference (or standard) sequence.

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WHAT TO EXPECT

- We expect that every person in our study will have a few results to learn over the course of the project, but we cannot predict ahead of time what health conditions your results will relate to.
- You will be offered different types of results through our project over time. All of the results you will receive today are inherited in the same way, which is why you are getting them together.
- The results you will receive today are those that may **affect your family members' health.** These results are not expected to affect your health, but could be relevant for family members. The results do not mean that you have an increased risk to develop these conditions yourself. Rather, they mean that an affected child could be born to someone in your family in the future.

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SECTION 2: GENETICS OVERVIEW

This section contains information on genetics.

It reviews the way genes are passed down in families and gives you information on how the conditions that you'll be receiving results for today are inherited.

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HOW GENES ARE INHERITED

7/23

- Your genes provide your body with instructions to grow, develop and run properly.
- Your genes were passed to you from your parents. For each gene, you have 2 copies - one from your mother and one from your father.
- The diagram shows how one gene is passed on from a mother and a father to the child. This is how you inherited each of your genes.

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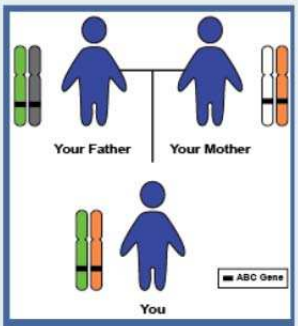

This picture shows how you inherited genes from your parents using a gene called *ABC*. The *ABC* gene is shown as black boxes in the picture. The gene is shown on a chromosome, which is the structure that passes genes from parents to children. You can see that one copy of your *ABC* gene came from your father and one came from your mother based on the shading of the chromosomes.

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HOW CHANGES IN GENES CAN AFFECT YOUR HEALTH

- Many of your genes have changes that either happened by chance or were inherited from your parents.
- Most of these changes do not cause health problems. Instead, they account for the differences among people.
- However, some of these changes can cause the gene to not work properly, which can lead to health problems.
- For most of your genes, you need only one working copy to avoid any related health problems. This means that you can be healthy even if you have one copy of the gene that does not work (because of a change). This is called a recessive inheritance pattern.
- **Today, you will learn about some gene changes that you have that are inherited in a recessive pattern. These are not expected to affect your health because we have only found a change that affects one copy of each gene.**

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SECTION 3: YOUR RESULTS AND THEIR SIGNIFICANCE

This section contains your results. In order to generate these results, over 1300 genes were reviewed. For each result, there are details on the name of the change and the condition it relates to.

Each condition is then described in further detail.

It also has information on how we expect your results might affect you and your family.

Finally, there is information on the testing limitations and our recommendations about what to do with these results.

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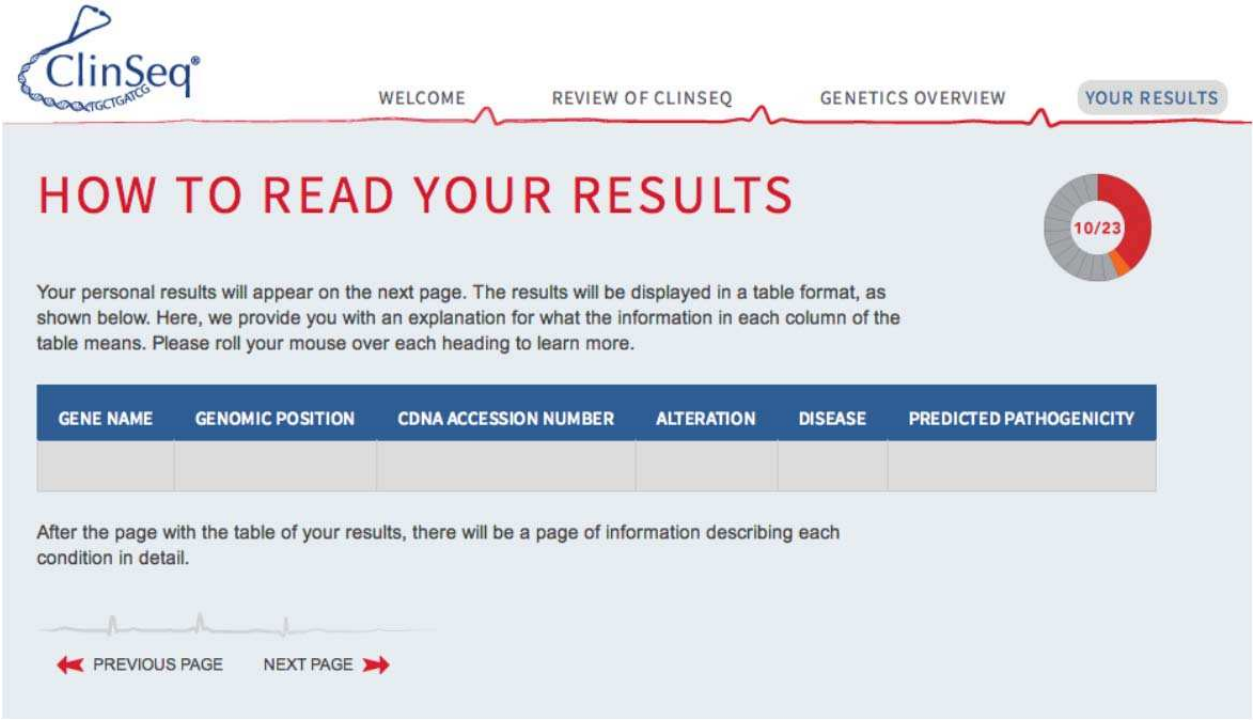

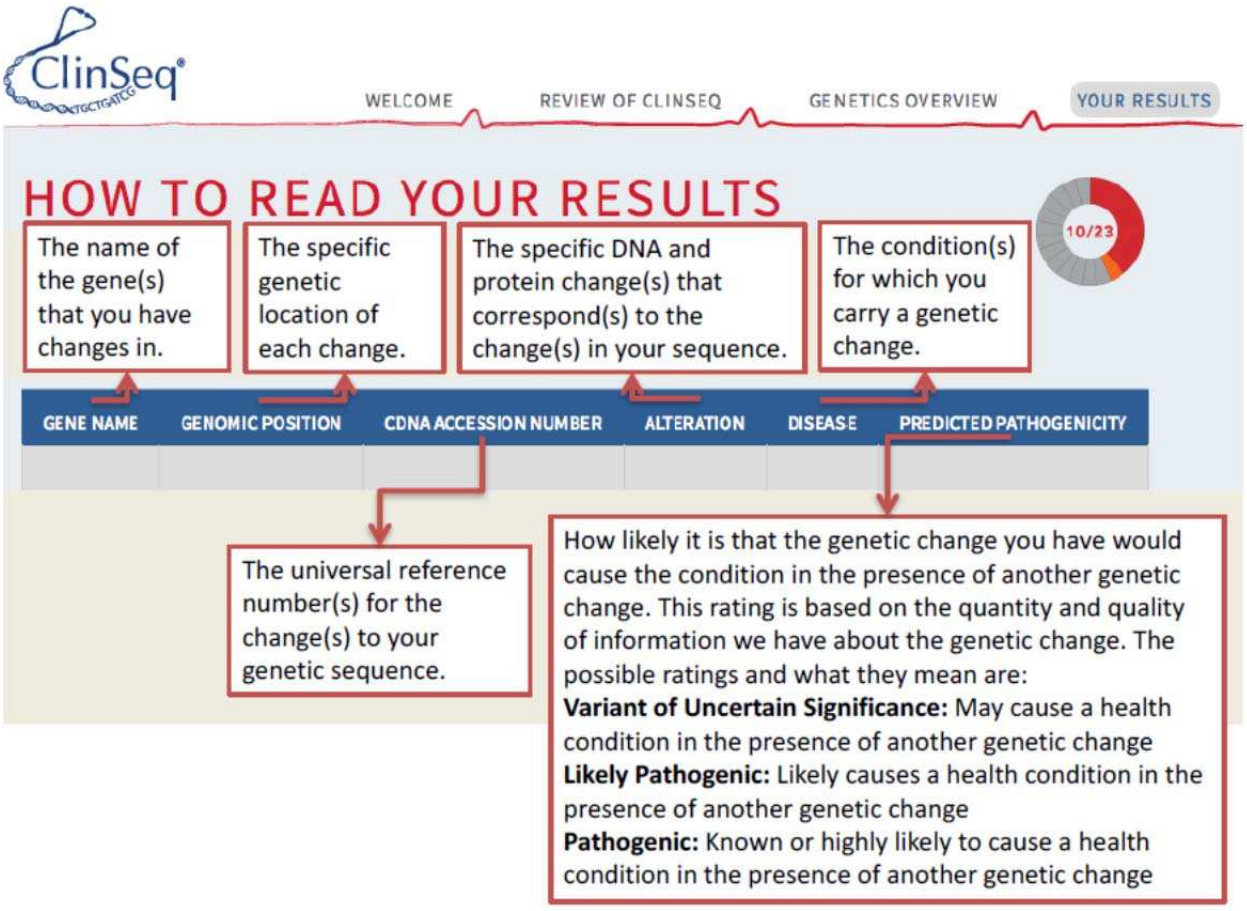

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YOUR RESULT REPORT

You were found to have the following genetic changes (alterations):

GENE NAME	GENOMIC POSITION	CDNA ACCESSION NUMBER	ALTERATION	DISEASE	PREDICTED PATHOGENICITY
ATP7B	chr13:g.52513198T>C	NM_000053.2	c.3688A>G; p.I1230V	Wilson disease	Variant of Uncertain Significance
SI	chr3:g.164737560T>C	NM_001041.3	c.3255-2A>G; splice site alteration	Sucrase-isomaltase deficiency, congenital	Likely Pathogenic
USH2A	chr1:g.216420460C>A	NM_007123.5	c.2276G>T; p.C759F	Retinitis pigmentosa, recessive, no hearing loss	Likely Pathogenic

Place your mouse over the heading at the top of each column or the disease name(s) or predicted pathogenicity rating(s) within the table to see more information about what they mean. The descriptions of each condition will also be repeated in the coming pages.

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BRIEF DESCRIPTION OF WILSON DISEASE

Wilson disease is an inherited disorder in which excessive amounts of copper accumulate in the body, particularly in the liver, brain, and eyes. Typically, signs and symptoms of Wilson disease first appear between the ages of 6 and 40, but most often begin during the teenage years. Liver disease is usually the initial feature of Wilson disease in people between the ages of 6 and 45. Signs and symptoms of liver disease include yellowing of the skin or the whites of the eye (jaundice), fatigue, loss of appetite, and abdominal swelling. Psychiatric or nervous system problems commonly occur in young adults with Wilson disease. Signs and symptoms of these problems can include clumsiness, trembling, difficulty walking, speech problems, deteriorating school work, depression, anxiety, and mood swings. In many individuals with Wilson disease, copper deposits form a green-to-brownish ring, called the Kayser-Fleischer ring, around the cornea (the front surface of the eye). Abnormalities in eye movements, such as the restricted ability to gaze upwards, may also occur.

Your chance to have a grandchild with this condition is:	42/30,000 (0.14%)
The average person's chance to have a grandchild with this condition is:	1/30,000 (0.0033%)

Please be aware that these are only average risks. Your chance to have an affected grandchild is based on how common the condition is, and knowing that you have a genetic change that may be related to this condition. Your personalized risk to have an affected grandchild depends on many factors that were not included in these calculations. If you wish to receive a personalized risk assessment based on your exact situation, we recommend that you seek out genetic counseling.

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WELCOME | REVIEW OF CLINSEQ | GENETICS OVERVIEW | YOUR RESULTS

WHAT THESE RESULTS MEAN FOR YOU AND YOUR CHILDREN

- For each of the conditions listed, you have one non-working copy of a gene. In genetics, **we say that you "carry" a change in the gene for each of the conditions listed.**
- If you are thinking about having (more) biological children, you and your partner may want to seek out genetic counseling based on this result. A genetic counselor can give you more information on your exact chances to have an affected child, and can coordinate testing for your partner to see if s/he also carries a change in the same gene(s) as you. The result of your partner's genetic testing would help determine the risk for you to have an affected child. If you do not plan to have (more) biological children, this testing is not recommended.
- It is unlikely that any of your children will become affected with these conditions if they are not already affected with them. This is because most of these conditions are diagnosed in early childhood, unless otherwise specified in the description(s).

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WHAT THESE RESULTS MEAN FOR YOUR GRANDCHILDREN

- There is a 1/2 (50%) chance that your children carry each of the genetic changes you have. If they carry these changes, it would mean that they have one working copy of the gene and are healthy.
- If any of your children carry these genetic changes, there is a chance that they could have a child affected by one of these conditions. Therefore, your results indicate some of the recessive conditions that your grandchildren could have. Because these conditions are so rare, it is unlikely that you will have a grandchild affected with any of these conditions.

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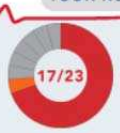

HOW COULD YOU HAVE A GRANDCHILD AFFECTED BY ONE OF THESE CONDITIONS?

Three things must happen for you to have an affected grandchild:

1. Your child must have inherited the genetic change from you
2. Your child's partner must have a change in the same gene
3. Both your child and their partner must pass on the changed copy of the gene to a child

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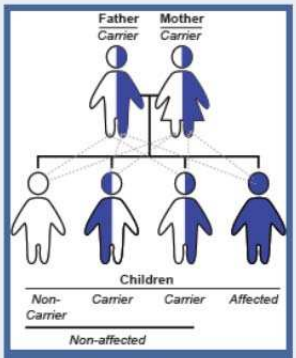

The diagram above shows the situation described in the text. Both parents in the family (your child and their spouse) are carriers for the condition. Every time they have a child, there are four possible outcomes, one of which is that they will have an affected child.

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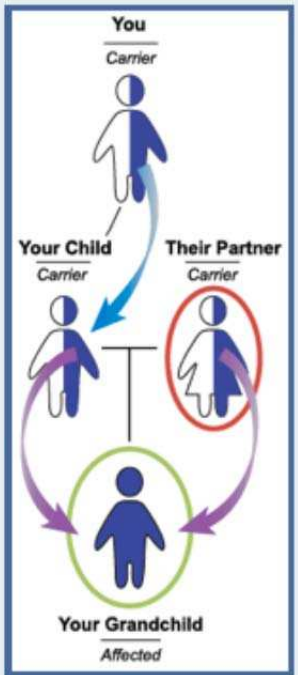
WHAT ARE THE CHANCES YOU WILL HAVE A GRANDCHILD AFFECTED WITH ONE OF THESE CONDITIONS?

In order for you to have a grandchild affected by one of the conditions, three things must happen. The chances for each of the three steps contribute to the overall chance for you to have an affected grandchild as shown. The coloring of the steps in the table below corresponds to the colors of each step portrayed in the figure.

STEPS	CHANCES OF THIS HAPPENING
1. Your child inherits the genetic change from you.	500/1,000 or 50%
2. Your child's partner carries a change **in the same gene**. The chances of this are based on how common the condition is.	Usually less than 20/1,000 or 2%
3. Both your child and their partner must pass on the changed copy of the gene to a child.	250/1,000 or 25%
Overall chance that all 3 steps occur and you have an affected grandchild.	Less than 2.5/1,000 or 0.25%*

** We have specified on the Condition Description pages if the chance of this is greater for any of your results.*



The four steps outlined to the left and above (shown as the blue arrow, red circle, purple arrows, and green circle) must all occur in order for your grandchild to be affected by any of the conditions that you carry.

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WELCOME | REVIEW OF CLINSEQ | GENETICS OVERVIEW | YOUR RESULTS

SUMMARY OF WHAT RESULTS MEAN FOR YOU AND YOUR FAMILY

- You "carry" the gene change for each condition listed on your report. None of the conditions listed are expected to affect you personally.
- Recessive conditions are usually diagnosed early in life, so your children are unlikely to be affected. If any of the conditions listed are diagnosed later in life, we have specified this in the condition descriptions
- It is most likely that you will not have a grandchild affected by any of these conditions. This was shown in the condition descriptions page(s), where your risk to have an affected grandchild was compared to the average person's risk. Please keep in mind that those risks were not tailored to your family. Anyone who wants to know their personalized risk should seek out genetic counseling.

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ClinSeq®

WELCOME | REVIEW OF CLINSEQ | GENETICS OVERVIEW | YOUR RESULTS

TESTING LIMITATIONS

- The testing we did cannot detect all possible genetic changes that may put you or your family at risk for health problems.
- Not all genetic changes can be interpreted based on current knowledge.
- It is likely that there are other conditions inherited in a recessive pattern that the sequencing and current knowledge cannot recognize.
- Therefore, the absence of a testing result does not rule out the possibility of having an affected family member in the future.

The genetic test only detects abnormalities that we currently know about

It's like searching for lost keys in the dark: we can only see where the light is shining at the moment. We may miss things that are beyond the light of our current knowledge

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ClinSeq®

WELCOME | REVIEW OF CLINSEQ | GENETICS OVERVIEW | YOUR RESULTS

RECOMMENDATIONS

- We will give you a printed copy of your result report to take home with you today. Approximately one month from now, we will send you a letter summarizing the information contained in this website.
- We encourage you to share this information with anyone in your family who is currently pregnant or planning a pregnancy, even if they don't have signs of these conditions or they don't run in your family. These individuals may want to seek out genetic counseling. A genetic counselor can provide more information on each of these conditions, calculate a personalized risk to have an affected child, and coordinate genetic testing, if needed. Genetic counselors can be found throughout the country by going to www.nsgc.org and using the "Find a Counselor" feature.
  - The best time for someone to be tested to see if they carry the gene is before they become pregnant so that they can know their risks.
  - People who carry the gene who want to have children may want to have their partner tested. If the partner is found to also carry the gene, the couple has a wide range of options to decrease their risks of having an affected child, including using sperm or egg donors or having prenatal diagnosis during a pregnancy.
- It is important to remember that these results only tell us that you are a carrier for these conditions - not that you have these conditions or are at risk to develop them in the future.

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ClinSeq®

WELCOME | REVIEW OF CLINSEQ | GENETICS OVERVIEW | YOUR RESULTS

RESULTS SUMMARY

- These results are not expected to impact your personal health and are unlikely to impact the health of any adult children you have.
- These results may have implications for the health of future generations in your family, such as grandchildren or great-grandchildren.
- Remember that we are continuing to look at your genetic sequence, and expect to have more results to share with you in the future. These results may have direct impacts on your health, and could pertain to a wide variety of health conditions - including both those that are treatable/preventable and those that are not.

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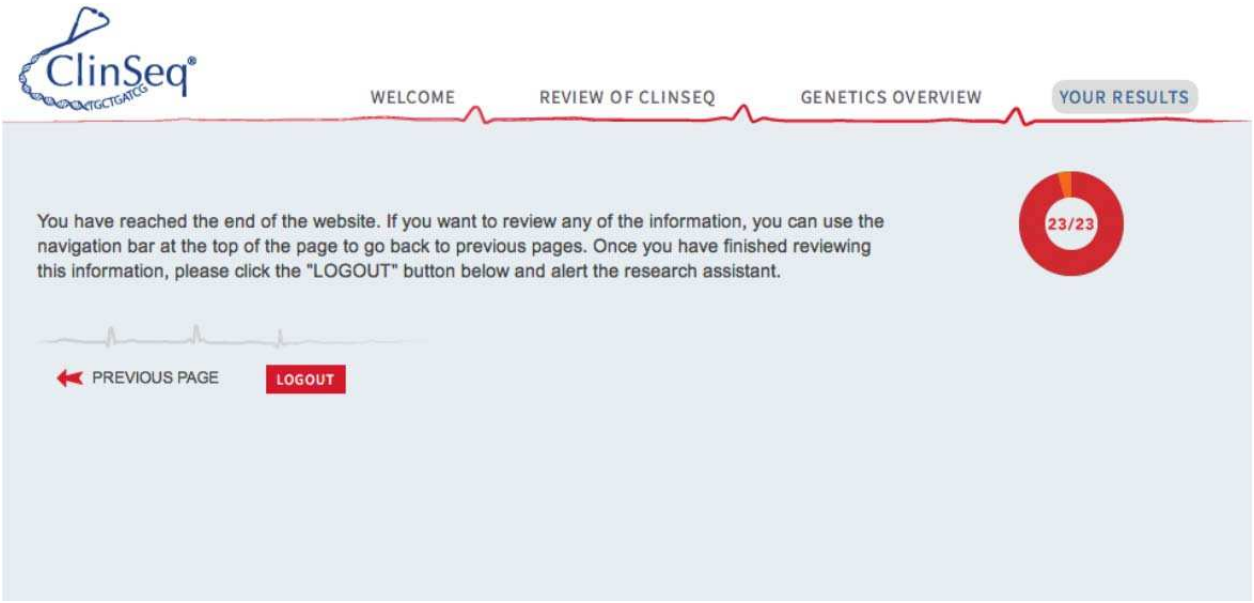

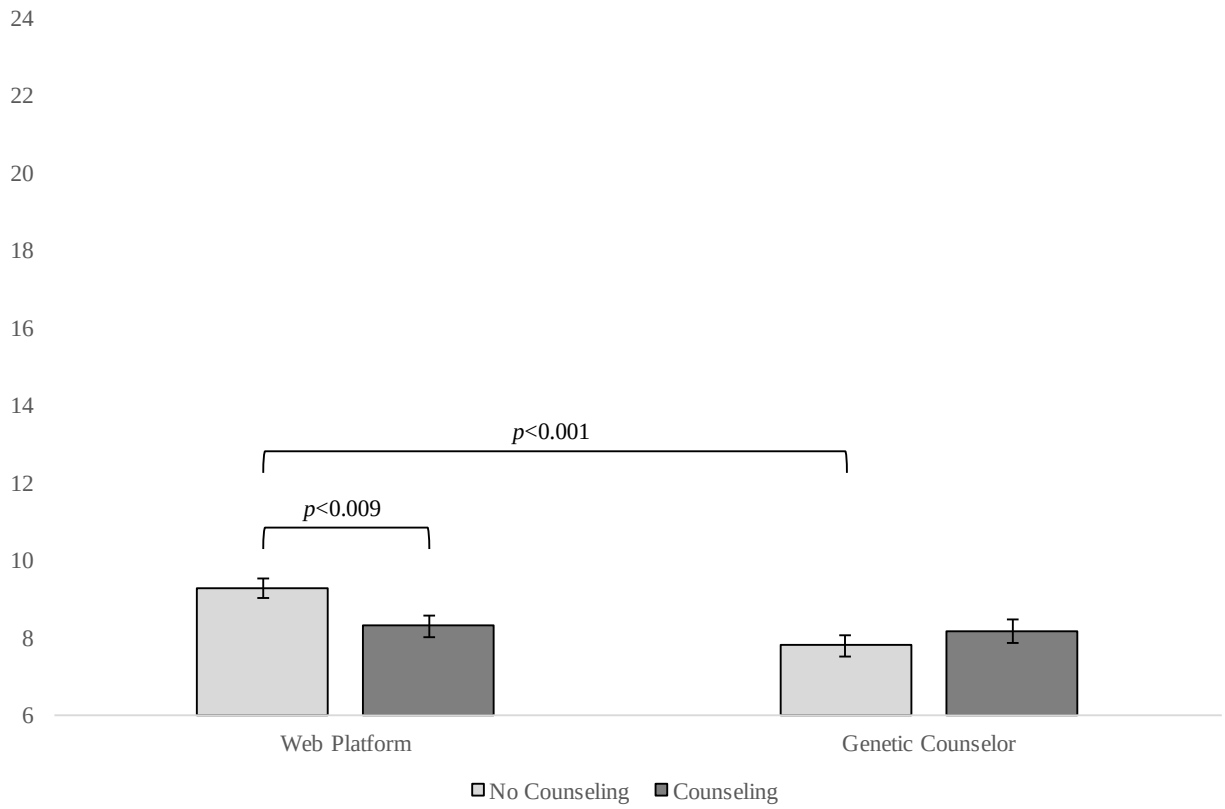

eFigure. Anxiety assessed immediately after counseling or no counseling. The contrast bars represent significant differences in means with respect to anxiety. Possible scores on this scale range from 6–24.

eTable 1. Participant Demographics and Clinical Characteristics of Responders and Nonresponders at T4.

		Responders (*n*=392)	Non-responders (*n*=67)
Characteristic	*Dichotomous Classification*	***n* (%)**	***n* (%)**
Gender	Male	217 (55.4)	29 (43.3)
	Female	175 (44.6)	38 (56.7)
Marital Status	Not in a marriage-like partnership	80 (21.2)	14 (21.5)
	In a marriage-like partnership	298 (78.8)	51 (78.5)
Household Income	Less than $100,000 per year	93 (24.8)	12 (18.7)
	More than $100,000 per year	282 (75.2)	52 (81.3)
Education	Less than a post-graduate degree	142 (37.4)	25 (38.5)
	Post-graduate degree	238 (62.6)	40 (61.5)
Race	White	364 (93.1)	62 (92.5)
	Non-white	27 (6.9)	5 (7.5)
Ethnicity	Hispanic or Latino	9 (2.3)	0 (0.0)
	Not Hispanic or Latino	380 (97.7)	67 (100.0)
Parental Status	No children	83 (23.6)	15 (25.4)
	At least one child	268 (76.4)	44 (74.6)
Results Returned	At least one “pathogenic”	292 (74.5)	57 (85.1)
	Zero “pathogenic”	100 (25.5)	10 (14.9)
	At least one “likely pathogenic”	125 (31.9)	30 (29.9)
	Zero “likely pathogenic”	267 (68.1)	47 (70.1)
	At least one “VOUS”	198 (50.5)	30 (44.8)
	Zero “VOUS”	194 (49.5)	37 (55.2)

eTable 2. Assessment of Fidelity to the Intervention in the Genetic Counselor Education Arm

Topic	Proportion reached adequate fidelity (%) N=106
1. Introduction to the RCT	
Review of genome sequencing and interpretation	95
Description of analysis done for RCT	96
2. Description of autosomal recessive inheritance	
Description of carrier status in proband--lack of symptoms	91
Description of carrier status in partner/children	91
Description of risk to grandchildren--lack of symptoms in healthy, adult children places focus on risks to grandchildren	85
Description of risk to grandchildren--both parents need to be carriers, both to pass on variants	84
3. Explaining sections of information on CLIA report	
Genomic position	92
Pathogenicity	97
Condition name	99
4. Variant results; Condition description and risk information for:	
1st result	96
2nd result	98
3rd result	97
4th result	97
5th result	100
6th result	100
7th result	100
5. Recommendations	
Sharing with reproductive-aged relatives	99
Reproductive-aged relatives recommended to have genetic counseling, ideally preconceptually	96
6. Limitations	
Absence of a result does not rule out having an affected family member in the future	98
Ongoing analysis of additional genes	83
7. Elicitation of questions by GC	87
8. Response to questions	100

PROTOCOL, AUGUST 30, 2013

Description of procedures

Potential participants will be chosen from individuals who have completed the ClinSeq® Social & Behavioral Baseline Survey (Survey IV, which provides baseline data for this study (T1), as well as other ancillary projects) and have available carrier testing results for disclosure. Results for all potentially-eligible participants will be CLIA validated, then participants will be contacted by a study team member by phone to inform them that they have carrier results available, confirm that they want to learn those results, describe and obtain consent for the study (see Appendix ZE for script), and schedule a date for results return. We hope to schedule participant visits at the rate of 10 per week.

Participants will return to the NIH CRC in order to receive their results. They will then be randomized to one of four arms of the study: 1) website-based results disclosure, 2) results disclosure by a genetic counselor, 3) website-based results disclosure + genetic counseling and 4) results disclosure by genetic counselor + genetic counseling. First, participants will have their results disclosed, either through the website or by a genetic counselor. Both results disclosure interventions will include information on: a) what a variant is, b) each variant found and the disease associated with it, c) what it means to be a heterozygote, recessive inheritance/risks to children, d) prevalence of variants and the lack of known interactions among the variants. The results disclosure interventions will be information-provision only (points a-d above), deferring questions (other than clarifications on points a-d) to the second part of the session. Participants will freely navigate the website after brief instruction by a research assistant. The genetics education session will be led by a Board-certified counselor in a process consistent with "usual care" genetics education. Results disclosure sessions will be limited to no more than 30 minutes (subject to change after pilot testing). Following the disclosure session, a follow up survey will be administered. There are separate versions of the survey for those who will be receiving genetic counseling (Appendix ZF-a, Intervention Survey T2 (Survey Via)) and those who will not (Appendix ZF-b, Intervention Survey T2 (Survey VIb)).

For the two groups that include genetic counseling, a session with a counselor will follow the disclosure education session. It will focus on the meaning and impact of the information, exploration of plans to use the information and any concerns the participants may have; structured by question prompts informed by cognitive behavioral theory. Genetic counseling will be limited to 30 minutes (subject to change after pilot testing). A second survey (Appendix ZG: Intervention Survey T3 (Survey VII)) will be administered following genetic counseling.

Two to eight weeks later, participants from all four groups will be administered a final survey (Appendix ZH: Intervention Survey T4 (Survey VIII) and will be sent visit summary letters. They will be reminded to take the survey three times via phone, secure email or other means of communication.

Describe questionnaires or other psychological instruments and estimate how long they will take to complete, and whether they address sensitive topics *(Enclose copies.)*

As described above, we propose to conduct a 2x2 randomized control to determine how a website compares to genetic counseling in facilitating understanding of carrier status identified through genomic sequencing. Participants will be given up to three surveys as part of their participation:

- Intervention Survey T2 (Appendix ZF, Survey VI-a) will be given immediately following the results disclosure session for those who are going to receive genetic counseling. The survey will assess knowledge, understanding, residual questions, and questions on participants' understanding of the possibility for false negative testing results. The measures consist largely of previously used and validated scales, as detailed in the Appendix. This survey will be administered at participants' clinical visits using Survey Monkey, a survey-design and data collection website. Alternatively, participants can complete the survey on paper if they prefer. The survey is expected to take no longer than 20 minutes.
- Intervention Survey T2 (Appendix ZF, Survey VI-b) will be given immediately following the results disclosure session for those who are not going on to receive psychosocial counseling. The survey will assess knowledge, understanding, residual questions, residual concerns, anxiety, satisfaction, decisional conflict, learning preferences, and questions on the participants' understanding of the possibility for false negative testing results. The measures consist largely of previously used and validated scales, as detailed in the Appendix. This survey will be administered at participants' clinical visits using Survey Monkey, a survey-design and data collection website. Alternatively, participants can complete the survey on paper if they prefer. The survey is expected to take no longer than 20 minutes.
- Intervention Survey T3 (Appendix ZG, Survey VII) will be given following the genetic counseling sessions in two groups, and will assess residual concerns, anxiety, satisfaction, decisional conflict, and preferences for having additional time with a GC to process the carrier results will be assessed. An open-ended question will explore what added value they found in the second portion of the session; they will be asked to rank the importance of the added value. Identification of elements of added benefit will be explored. The measures consist largely of previously used and validated scales, as detailed in the Appendix. This survey will be administered at participants' clinical visits using Survey Monkey, a survey-design and data collection website. Alternatively, participants can complete the survey on paper if they prefer. The survey is expected to take no longer than 20 minutes.
- Intervention Survey T4 (Appendix ZH, Survey VIII) will be given two to eight weeks following the visit and will assess knowledge of carrier status, understanding of inheritance, satisfaction with the intervention and decisional conflict about learning results, disclosure of information, impact of results (MICRA) and engagement with ClinSeq. This survey will be administered online using Survey Monkey, a survey-design and data collection website. Alternatively, participants can complete the survey on paper if they prefer. The survey is expected to take no longer than 15 minutes. Participants will be reminded to take the survey up to three times using phone, secure medical email, mailings to their home, or other approaches.

Genetic counseling (By whom, would counseling happen in person, will understanding be assessed?)

Participants in this study will be randomized to one of four study groups for return of results: 1) website-based results disclosure, 2) results disclosure by a genetic counselor, 3) website-based results disclosure + genetic counseling and 4) results disclosure by genetic counselor + genetic counseling. Therefore, some participants will not have immediate access to a genetic counselor as part of the randomization scheme, and other participants will have access to a genetic counselor in only a limited capacity (e.g. a session focused on educational and not psychosocial components of results). Participants will be offered full access to a genetic counselor at the end of the study, following the 2-3 week post-result survey. If a participant expresses an urgent need for genetic counseling prior to that point, they will be removed from the intervention study and will be scheduled for a genetic counseling session.

Estimated number of participants, enrollment ceiling, and anticipated enrollment by year.

Potential participants will be chosen from individuals who have completed the ClinSeq® Social &Behavioral Baseline Survey (Survey IV), which provides baseline data for this study (T1), as well as other ancillary projects. In order to be eligible, participants must have carrier testing results available from sequence data analysis, and must be willing to receive their results and participate in the intervention study. The initial target enrollment for this study is 400 participants; however more may be recruited to allow us to have a total of 400 individuals complete the study after attrition. Those participants will be enrolled at the rate of 10 per week over the coming year.

Description and justification of clinical inclusion/exclusion criteria. (affected individuals, family members, controls? Define clinical criteria: Will this determination be made by review of prior records or will a screening evaluation be performed? Justify population choice in regard to age, gender, ethnicity, prisoners, pregnant women, fetuses, people with impaired decision-making ability, healthy volunteers, lab personnel)

In order to be eligible for inclusion in this project, a participant must have completed ClinSeq® Survey IV (Appendix ZB), have carrier testing results available from whole exome sequence data analysis, and must consent to participate in a randomized control trial of results return. Only individuals who have completed the survey will be eligible for participation because this survey provides baseline (pre-result return) data, which is critical for the planned analyses. Similarly, only participants with carrier testing results will be included in the study since the project is focused on return of these results only.

Description of recruitment strategies (How participants will be identified; include copies of recruitment advertisements.)

Participants for the Intervention Study will be recruited from the population of participants who have completed Survey IV (Appendix ZB), have carrier testing results available from whole exome sequence analysis, and are willing to give consent to participate in a randomized control trial. All eligible participants will be contacted via phone in order of survey completion to assess

their interest and obtain verbal consent. Clinic visits will subsequently be scheduled in order of response to our phone contact.

Description of statistical considerations and/or analytic plan (Sample size and power calculations, methods of analysis, criteria for significance, if this applies.)

This study was powered based upon outcomes of two integrated studies. 500 participants, 125 in each group, would provide sufficient power to detect a main effect defined as a difference of 2 points on the 7 point attitudes scale or 3+ points on the 12 point intentions scale and to assess interaction effects. If there were 300 participants, it would take a difference of 4+ points on the intentions scale to demonstrate a main effect. The initial target for this study will be 400 participants.

Descriptive analyses will be used to assess response frequencies and distributions. Differences in responses to key variables will be assessed using pre-post comparisons of responses. Bivariate analyses will help to clarify relationships among independent variables. Multivariate regression will determine the relative contribution of significantly correlated variables to the variance in *understanding carrier status* across the four groups. Further, responses to open-ended questions will be coded and analyzed for prominent themes or patterns used to describe elements of genetic counseling. Statistical consultation by Abt Associates will be sought for consultation and any further analyses.

Psychological harms (misunderstanding, anxiety, self-esteem, depression)

It is possible, though very unlikely, that participation in the intervention study could cause psychological distress. If this is recognized, we will provide brief, short term counseling, offer the subject a follow-up counseling visit at the NIH and/or refer them to their primary care provider for further support.

Who will obtain consent *(PI, study coordinator, and primary physician)?* If collaborators who are not designated as co-investigators will be obtaining consent, both the PI and the collaborator who is obtaining consent should sign the consent form.

Verbal consent for the project will be obtained over the telephone by a research staff member, following a script (see Appendix ZE).

PROTOCOL AMENDMENT, AUGUST 5, 2014

Description of procedures

Added Text:

Six months after receiving their result, participants from all four groups will be administered a final survey (Appendix ZK: Intervention Survey T5). They will be reminded to take the survey up to three times via phone, secure email, or other means of communication.

Describe questionnaires or other psychological instruments and estimate how long they will take to complete, and whether they address sensitive topics *(Enclose copies.)*

Added Text:

- Intervention Survey T5 (Appendix ZK, Survey IX) will be given six months following the visit and will assess a number of social and behavioral constructs related to return of results. This survey will be administered online using Survey Monkey, a survey-design and data collection website. Alternatively, participants can complete the survey on paper if they prefer. The survey is expected to take no longer than 20 minutes. Participants will be reminded to take the survey up to three times using phone, secure medical email, mailings to their home, or other approaches.