PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Scientific Title: A protocol for Health Risk Information Technology-Assisted Genetic Evaluation (HeRITAGE): A randomized controlled trial of digital genetic cancer risk assessment in a diverse underserved gynecology clinic
AUTHORS	Bull, Leslie; Webster, Emily M.; McDougale, Auja; Howard, Denise; Ahsan, Muhammad Danyal; Levi, Sarah; Grant, Benjamin; Chandler, Isabelle; Christos, Paul; Sharaf, Ravi N.; Frey, Melissa

VERSION 1 - REVIEW

REVIEWER NAME	***Shane-Carson, Kate P.***
REVIEWER AFFILIATION	The Ohio State University, Division of Human Genetics
REVIEWER CONFLICT OF INTEREST	I have published the following manuscript which is a related topic area and also utilizes the Care portal for patient identification for hereditary cancer genetic testing: Shane-Carson KP, Smith D, Smith A, Seeley C. Retrospective chart analysis to determine the impact of a patient-facing digital risk stratification tool combined with a clinical screener for hereditary cancer genetic risk assessment triage in a community oncology clinic. J Community Genet. 2023 Oct 27. doi: 10.1007/s12687-023-00687-3. Epub ahead of print. PMID: 37889419.
DATE REVIEW RETURNED	15-Dec-2023

GENERAL COMMENTS	(1) Please clarify when patients will provide consent (at home prior to the appointment? once the arrive at the physician office in the waiting room? other?). Also provide more details about how the patients will be contacted to provide informed consent and who will be obtaining the informed consent. (2) Please clarify when patients in the intervention arm are completing the CARE chatbot (a) is this something they are sent prior to the appointment (and if so, how long prior to the appointment? one week? one day?). (b) are patients completing this in the waiting room at the physician office prior to the appointment? (c) if a patient in the intervention arm does not complete the care assessment prior to the appointment with their physician, are they re-contacted or provided a reminder? If so, please describe that process. (3) Line 113 within the Introduction notes "limited appointment time with inadequate family history collection" and line 275 of the discussion notes "...address common genetic cancer risk assessment barriers such as limited appointment time. Please include in the discussion how they study design and results will be able to evaluate/address issues with limited provider time/inadequate history collection. As presented, it is clear that the CARE model (since it references NCCN guidelines) will be able to facilitate identification of patients eligible for genetic testing based on their reported family history. The study as designed would also be able to identify, through retrospective review, if patients in the control arm reported family history of cancer to their providers that met NCCN criteria for testing, but that they were not referred for testing. However, I do not see anything that describes a method to evaluate the family history collected in the control arm, to assess if an inadequate family history was taken due to appointment constraints (i.e. would patients in the control arm then take the CARE assessment after their appointment with the provider, and would family history reporting then be compared, to determine if providers missed accruing/documenting complete family histories?). In summary, it is clear that this study is designed to assess the rate that providers are accurately referring patients for genetic testing based on reported family. What is not clear is how this study would assess whether providers are obtaining/documenting a complete family history or not due to appointment constraints. Either include the methods for this evaluation, or remove this potential outcome from the manuscript. (4) The Discussion paragraph beginning at line 262 discusses how this site was chosen for the study due to patients underrepresented in genetics research, including race, ethnicity, insurance status, and other social determinants of health. It is also noted in lines 242-243 of the discussion that the anticipated study population for the HeRITAGE study is anticipated to be more diverse that other previously reported studies. As such, please note the current reported mix/percentages of ethnicities of the patient population typically seen at this clinic site (for example, 30% white, 20% black, 40% Hispanic, 5% Asian, 5% other). Also, it is noted in multiple places throughout the paper the inability to recruit non-English speaking participants. Based on the reported ethnic mix of the patients currently seen at the study site, for what is known of the percentage of non-English speaking patients, how might this affect your ability to recruit patients of diverse ethnic backgrounds to your study (do a majority of the non-white patients speak English, or will a majority of them end up being excluded from the study due to a language barrier?)

REVIEWER NAME	***Speiser, Dorothee***
REVIEWER AFFILIATION	Charite Medical Faculty Berlin
REVIEWER CONFLICT OF INTEREST	Na
DATE REVIEW RETURNED	19-Dec-2023

GENERAL COMMENTS	Thank you for the opportunity to review this very interesting and relevant study protocol. I am very interested in the results of this trial.

REVIEWER NAME	***Bombard, Yvonne***
REVIEWER AFFILIATION	Li Ka Shing Knowledge Institute, St. Michaels' Hospital
REVIEWER CONFLICT OF INTEREST	Dr. Yvonne Bombard is the CEO and Co-Founder of Genetics Adviser Inc.
DATE REVIEW RETURNED	26-Feb-2024

GENERAL COMMENTS	Thank you for the opportunity to review this protocol paper of the HeRITAGE study, a randomized controlled trial to compare the number of eligible patients that are recommended genetic testing by the digital tool (CARETM) versus clinicians. Study Title - Consider adding the word 'protocol' in the title to make it clearer what this paper is about. Abstract - No mention of qualitative interviews nor of secondary and exploratory outcomes. Strengths and Limitations Section - Several comments were made about the generalizability of the results to other practices due to the wide eligibility criteria. The authors should consider tempering their language to acknowledge the limits of the generalizability of their results considering recruitment will only be happening from one gynecology clinic with no efforts to ensure diversity of participants recruited. This should be carried through to the limitations as well. Methods and Analysis: Trial Design - The design of multi-method or mixed methods should be described as both an RCT and interviews will be conducted. - A description of qualitative data methods, data collection and analysis are missing. - Further clarification of what is meant by 'mainstream genetic counseling and testing' and whether this is happening for both control and intervention arms would be helpful. - There are additional features available in the intervention beyond usual care but those are not accounted for in the trial design and evaluation. In the intervention arm, there is a risk assessment plus pre-test counselling consisting of optional educational videos. Control is clinician-driven interview and assessments. The additional pre-test counselling and the variability in patients viewing the videos confound some of the outcomes (ie. quality and quantity of family history identification). - Clarify whether oncologists or genetics clinicians are conducting the 'clinician driven interview and assessments'. - The dates of the study are missing and should be included following the journal's guidelines. Participants - The paper can benefit from additional details regarding the sampling pool, the sampling approach and how eligible individuals will be recruited or informed about the study, by whom, and at what time point they will be approached etc. - Eligibility criteria based on the NCCN is confusing and seems to overlap with the primary outcome of the trial (identifying eligible patients). - If possible, consider including non-English speakers and low-tech options or offering a tablet at enrollment to support the inclusion of a more diverse sample. Primary Endpoints - The trial does not measure accuracy (whether people are objectively eligible for testing) of the intervention compared to usual care. In this study, the comparator seems to be the discordance between the digital tools risk assessment vs. that of the clinician but does not account for whether either approaches identify eligible patients for testing. The intervention should also be compared in terms of its concordance to the decisions made by the clinician. - The uptake of genetic testing should be uncoupled from the trial of

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Ms. Kate P. Shane-Carson, The Ohio State University
Comments to the Author:

(1) Please clarify when patients will provide consent (at home prior to the appointment? once the arrive at the physician office in the waiting room? other?). Also provide more details about how the patients will be contacted to provide informed consent and who will be obtaining the informed consent.

Patients will be screened and consented in the clinic waiting area by study personnel prior to their appointments. This information has been added to lines 153-154.

(2) Please clarify when patients in the intervention arm are completing the CARE chatbot (a) is this something they are sent prior to the appointment (and if so, how long prior to the appointment? one week? one day?). (b) are patients completing this in the waiting room at the physician office prior to the appointment? (c) if a patient in the intervention arm does not complete the care assessment prior to the appointment with their physician, are they re-contacted or provided a reminder? If so, please describe that process.

Patients are given opportunity to complete the tool in the waiting room and exam room prior to provider visit. However, patients are not mandated to complete the tool. Edits made to lines 166-168.

(3) Line 113 within the Introduction notes "limited appointment time with inadequate family history collection" and line 275 of the discussion notes "...address common genetic cancer risk assessment barriers such as limited appointment time. Please include in the discussion how they study design and results will be able to evaluate/address issues with limited provider time/inadequate history collection. As presented, it is clear that the CARE model (since it references NCCN guidelines) will be able to facilitate identification of patients eligible for genetic testing based on their reported family history. The study as designed would also be able to identify, through retrospective review, if patients in the control arm reported family history of cancer to their providers that met NCCN criteria for testing, but that they were not referred for testing. However, I do not see anything that describes a method to evaluate the family history collected in the control arm, to assess if an inadequate family history was taken due to appointment constraints (i.e. would patients in the control arm then take the CARE assessment after their appointment with the provider, and would family history reporting then be compared, to determine if providers missed accruing/documenting complete family histories?). In summary, it is clear that this study is designed to assess the rate that providers are accurately referring patients for genetic testing based on reported family. What is not clear is how this study would assess whether providers are obtaining/documenting a complete family history or not due to appointment constraints. Either include the methods for this evaluation, or remove this potential outcome from the manuscript.

We agree with Ms. Shane-Carson that the trial is not intended to evaluate comprehensiveness of family history, and that the inclusion of such in the Introduction and Discussion is outside the scope of this manuscript. We have removed reference to inadequate family history collection from the

Introduction and the Discussion.

(4) The Discussion paragraph beginning at line 262 discusses how this site was chosen for the study due to patients underrepresented in genetics research, including race, ethnicity, insurance status, and other social determinants of health. It is also noted in lines 242-243 of the discussion that the anticipated study population for the HeRITAGE study is anticipated to be more diverse that other previously reported studies. As such, please note the current reported mix/percentages of ethnicities of the patient population typically seen at this clinic site (for example, 30% white, 20% black, 40% Hispanic, 5% Asian, 5% other). Also, it is noted in multiple places throughout the paper the inability to recruit non-English speaking participants. Based on the reported ethnic mix of the patients currently seen at the study site, for what is known of the percentage of non-English speaking patients, how might this affect your ability to recruit patients of diverse ethnic backgrounds to your study (do a majority of the non-white patients speak English, or will a majority of them end up being excluded from the study due to a language barrier?)

Thank you for this point. Our research group has previously conducted work within the same clinic, with the following breakdown of racial and ethnic self-identification: Hispanic (44%), non-Hispanic Black (28%), and non-Hispanic White (18%). Patients most commonly had Medicaid (76%) or a New York state–funded insurance (13%). We have added a reference to this published work which demonstrates racial and ethnic diversity within the study site. (Webster EM, Am J Obstet Gynecol. 2024 ;doi:10.1016/j.ajog.2024.01.009). Lines 396-399.

Within our manuscript, we acknowledge the limitation regarding recruitment of only English speaking and reading patients. Expanding the tool to facilitate use among patients speaking and reading other languages is an active area of work in our research group. Lines 339-342.

Reviewer: 2

Dr. Dorothee Speiser, Charite Medical Faculty Berlin
Comments to the Author:

Thank you for the opportunity to review this very interesting and relevant study protocol. I am very interested in the results of this trial.

We appreciate Dr. Speiser’s comments.

Reviewer: 3

Dr. Yvonne Bombard, Li Ka Shing Knowledge Institute, St. Michaels' Hospital, University of Toronto Institute of Health Policy Management and Evaluation
Comments to the Author:
Thank you for the opportunity to review this protocol paper of the HeRITAGE study, a randomized controlled trial to compare the number of eligible patients that are recommended genetic testing by the digital tool (CARETM) versus clinicians.

Study Title
- Consider adding the word ‘protocol’ in the title to make it clearer what this paper is about.

The title has been changed to “A Protocol for Health Risk Information Technology-Assisted Genetic Evaluation (HeRITAGE): A randomized controlled trial of digital genetic cancer risk assessment in a diverse underserved gynecology clinic” (lines 1-3). A public title has been added: A protocol for a randomized controlled trial evaluating the use of a digital genetic cancer risk assessment tool in a

gynecology clinic (lines 5-6)

Abstract
- No mention of qualitative interviews nor of secondary and exploratory outcomes.

A more comprehensive discussion of outcomes have been added to the abstract (lines 76-81).

Strengths and Limitations Section
- Several comments were made about the generalizability of the results to other practices due to the wide eligibility criteria. The authors should consider tempering their language to acknowledge the limits of the generalizability of their results considering recruitment will only be happening from one gynecology clinic with no efforts to ensure diversity of participants recruited. This should be carried through to the limitations as well.

The manuscript has been edited to temper our statements regarding generalizability, and more directly acknowledge these limitations in the Discussion section (lines 333-343)

Methods and Analysis:

Trial Design
- The design of multi-method or mixed methods should be described as both an RCT and interviews will be conducted.

After discussion, the authors feel that a randomized controlled trial best represents the trial. Non-randomized portions of this study represent only exploratory outcomes. We have decided to remove the non-randomized portions of the study from this protocol to allow for greater focus and detail to be included to describe the randomized portions which comprise our primary and secondary objectives.

- A description of qualitative data methods, data collection and analysis are missing.

After discussion, we have decided to remove discussion of the qualitative interviews from this protocol, as this is an exploratory aim not directly related to the randomized controlled design of this study and warrants its own dedicated and detailed protocol description.

- Further clarification of what is meant by ‘mainstream genetic counseling and testing’ and whether this is happening for both control and intervention arms would be helpful.

Mainstream genetic counseling and testing is a widely described and accepted approach to genetic testing in which pre-test counseling and testing is performed by a non-genetics provider (in this case, by the gynecologic provider). This is occurring in both arms and is not part of the randomized intervention.

We have clarified the text in lines 179-181.

- There are additional features available in the intervention beyond usual care but those are not accounted for in the trial design and evaluation. In the intervention arm, there is a risk assessment plus pre-test counselling consisting of optional educational videos. Control is clinician-driven interview and assessments. The additional pre-test counselling and the variability in patients viewing the videos confound some of the outcomes (ie. quality and quantity of family history identification).

The primary objective of the trial is to assess the impact of this digital risk stratification tool on the

likelihood of patients receiving genetic counseling (and secondary objective – the likelihood of patients receiving genetic testing). The optional educational videos that are included in this tool do not confound our outcomes, as we are interested in the impact of the tool as a whole.

- Clarify whether oncologists or genetics clinicians are conducting the 'clinician driven interview and assessments'.

The primary gynecologic provider is conducting their usual new patient interview and assessment. This has been clarified in lines 174-176.

- The dates of the study are missing and should be included following the journal's guidelines.

The manuscript has been updated: "Enrollment is anticipated to be conducted between January 2023 and December 2024. " (Lines 156-157).

Participants
- The paper can benefit from additional details regarding the sampling pool, the sampling approach and how eligible individuals will be recruited or informed about the study, by whom, and at what time point they will be approached etc.

We have clarified these points in the text as follows: "Patients will be screened and approached by study personnel for consent in the clinic waiting room prior to scheduled appointments. All patients scheduled for new patient appointments during periods of study personnel availability are screened." (Lines 153-155)

- Eligibility criteria based on the NCCN is confusing and seems to overlap with the primary outcome of the trial (identifying eligible patients).

Eligibility for genetic testing based on NCCN criteria has no bearing on eligibility for enrollment into the study. Patients who have already underwent genetic testing (regardless of their eligibility for genetic testing based on NCCN criteria) were excluded from the study. Including patients who have already been tested for hereditary cancer syndromes would negate the possibility of the patients achieving the primary outcome of receiving counseling regarding genetic testing (as the patients have already been tested, this counseling would be obsolete).

- If possible, consider including non-English speakers and low-tech options or offering a tablet at enrollment to support the inclusion of a more diverse sample.

We agree with the importance of including non-English speaking patients. At this time, additional efforts are underway to explore the effect of the smartphone-based tool in non-English speaking populations (lines 339-342) within our research group.

Primary Endpoints
- The trial does not measure accuracy (whether people are objectively eligible for testing) of the intervention compared to usual care. In this study, the comparator seems to be the discordance between the digital tools risk assessment vs. that of the clinician but does not account for whether either approaches identify eligible patients for testing. The intervention should also be compared in terms of its concordance to the decisions made by the clinician.

The final determination for genetic testing eligibility based on NCCN guidelines will be made by study personnel review of electronic record. Charts are also reviewed for whether these eligible patients were recommended for genetic testing by their gynecology provider.

This process has been clarified in in the text lines 183-188.

- The uptake of genetic testing should be uncoupled from the trial of a digital risk assessment tool since the tool itself should not be influencing whether or not the patients decide to pursue testing but rather only identifying who is eligible/at risk. The uptake of genetic testing is likely going to be determined by other social, medical, SDoH and personal factors.

We agree it is a possibility that the tool does not affect the uptake of genetic testing. We do not make any hypotheses to this regard. However, we are including the outcome of genetic testing as we feel this downstream outcome is of interest to readers.

Data collection
- A clearer description of data collection methods and details of the measures chosen for each outcome and whether they are validated measures should be listed.

With regard to the pre- and post-appointment surveys, the surveys will be distributed to participants via paper. Responses will be entered into REDCap database by study personnel. Detailed description of the pre- and post-appointment surveys have been added to the manuscript. (Lines 190-212)

- Further, the different demographics and social determinants of health that will be collected should be specified clearly; and whether there will be an evaluation or analysis of diversity dimensions, per their aims.

We have clarified our measures of social determinants of health, including the use of validated Health Leads Screening Toolkit and the Healthcare Distrust Scale. Health literacy, which is closely associated with social determinants of health, are also being evaluated. The results of these measures will be reported in the study.

- A clearer description of the type of questions that will be included in the post-test survey to understand attitudes toward results would be helpful.

We have updated the manuscript to include more detailed information regarding the survey: “The post-appointment survey will assess patient genetic cancer risk assessment experience and distress using the Hospital Anxiety and Depression Scale20 and NCCN Guidelines® Distress Thermometer,17 in which patients provide a numeric 0-10 value correlating with subjective distress, as well as 5-point Likert scale items (strongly agree / agree / neither agree or disagree/ disagree / strongly disagree) developed for the study to assess experience. Items include “I was satisfied with the genetic cancer assessment” and “The genetic cancer assessment was a waste of time.” (lines 201-207)

- There are little to no details on how the uptake of genetic testing will be recorded nor the timeframe the patients will be followed for (ie. patients may decide to undergo genetic testing a few months later or at a later stage (ie. after a surgery).

All data will be collected by a combination of the digital tool and paper forms and will then be encoded in REDCap by study personnel (lines 210-212). Patients will be considered to have undergone genetic testing for the purposes of this study if they complete genetic testing within 1 month of their appointment (lines 209-210).

Sample Size
- The sample size calculation requires further justification. It is not clear what difference the authors are planning to detect and what minimal clinically important difference will be used.

Based on an anticipated 5% rate of genetic testing counseling among eligible patients, the study aims to enroll 50 patients in each arm to allow for 80% power with two-tailed alpha of 5% to detect a 20% difference in proportion of eligible patients recommended for genetic testing. This has been added to the abstract in lines 74-76 and to the manuscript in lines 241-247.

Randomization and Blinding
- Clarification about who will conduct the randomization and when could be helpful.

Participants will be randomized 1:1 to either the digital tool arm or usual care arm via a preset computer-generated randomization scheme accessed through REDCap. After enrollment, patients are randomized and informed of their study arm. Clinicians are not blinded to enrollment arm as a tool-generated risk assessment summary is received for participants randomized to the intervention arm. (Lines 251-255).

- Details on any restrictions should be included.

There are no restrictions.

Analysis
- There is no description of how qualitative data will be analyzed and how this data will be combined with the quantitative data.

After discussion, we have decided to remove discussion of the qualitative interviews from this protocol, as this is an exploratory aim not directly related to the randomized controlled design of this study and warrants its own dedicated and detailed protocol description.

Patient and Public Involvement
- The section's subheading does not clearly explain the content of the section.

We have clarified the content of the section. (line 272). Neither patients nor public have been involved in the design or implementation of this study.

- Please update the reference for the pilot study as it is not correct.

References have been reviewed.

Ethics and Dissemination
- Potential Conflicts of Interest with Ambry Genetics should be addressed.

The authors do not endorse any conflicts of interest. This has been added to line 286.

Discussion:
- The authors hypothesize that the implementation of a digital risk assessment tool in a gynecology clinic given the longstanding barriers to genetic cancer risk assessment will identify more patients as eligible for testing which will subsequently lead to a higher rate of patients being recommended testing. The authors should acknowledge that a major barrier for underrepresented individuals is access and the ability to attend to these clinics will not be addressed by implementing a digital health tool that will only be available after arriving at the clinic.

We agree and have added the following text to the manuscript: "HeRITAGE requires in-person

appointment attendance for recruitment, and does not address physical access to clinic spaces as a barrier to genetic testing." (lines 342-343)

- The authors assert that their proposed study population will differ from Loving's primarily non-Hispanic White (78.3%) study sample from a single imaging center. However, their current eligibility criteria and sampling do not promote diversity since they are recruiting from a single gynecology clinic in an urban center without additional efforts to reach a more heterogeneous and diverse participant pool.

Our research group has previously conducted work within the same clinic, with the following breakdown of racial and ethnic self-identification: Hispanic (44%), non-Hispanic Black (28%), and non-Hispanic White (18%). Patients most commonly had Medicaid (76%) or a New York state–funded insurance (13%). We have added a reference to this published work which demonstrates racial and ethnic diversity within the study site. (Webster EM, Am J Obstet Gynecol. 2024 ;doi:10.1016/j.ajog.2024.01.009) Lines 396-399.

- The authors mention that further downstream data, such as the rate of genetic testing, will also be reported. These should be more clearly outlined in the methods and a clear description of what other downstream data will be collected should be described.

In the context of the lines quoted by the reviewer, downstream data refers to receiving counseling for genetic testing and receiving genetic testing, as made clear in the preceding sentence [referring to another study]: "Downstream data on the impact of the tool, such as number of patients who were appropriately recommended for genetic testing or received genetic testing was not included in the publication…". In the line quoted by the reviewer, we note that our study evaluated both receipt of counseling and receipt of genetic testing. Lines 313-316

- The authors say that their data may also reveal vulnerable populations, such as those less comfortable with technology, that may require additional attention should a smartphone-based tool be incorporated as the standard of care. The authors should clarify how they will assess these outcomes and which measures will be used. There is also no mention of how this data will be collected.

We agree this statement may be misleading regarding the objectives of the study. The statement has been removed.

Figures:
- Consider embedding Figures 2A and 2B into Figure 1.
- More detailed descriptions in the captions for Figures 1 and 2 will be helpful.

Figure descriptions have been updates to include more details. (Lines 351-352 and 354-356)

Minor Comments:
- Suggest creating an intervention arm sub-heading and Control arm sub-heading to define more clearly what is happening in each step.

We have broken up the intervention into more readable paragraphs to help define more clearly the content of each arm.

VERSION 2 – REVIEW

REVIEWER NAME	***Shane-Carson, Kate P.***

REVIEWER AFFILIATION	The Ohio State University, Division of Human Genetics
REVIEWER CONFLICT OF INTEREST	Na
DATE REVIEW RETURNED	12-Jun-2024

GENERAL COMMENTS	All of my suggested revisions have been addressed. I have no further suggestions for this manuscript. I look forward to seeing the results of this study!

REVIEWER NAME	***Bombard, Yvonne***
REVIEWER AFFILIATION	Li Ka Shing Knowledge Institute, St. Michaels' Hospital
REVIEWER CONFLICT OF INTEREST	Dr. Yvonne Bombard is the CEO and Co-Founder of Genetics Adviser Inc. Daniel Assamad - I have no conflict of interest to declare.
DATE REVIEW RETURNED	22-Jul-2024

GENERAL COMMENTS	Thank you for the opportunity to review the revision of this protocol paper of the HeRITAGE study, a randomized controlled trial to compare the number of eligible patients that recommended genetic testing by the digital tool (CARETM) compared to clinicians. Overall, all our comments were adequately addressed in the revisions made. This version of the manuscript reads much clearer than the original version. Comments: Line 178: Mention of what will be documented (ie. decision change, reason, etc.) in situations where the clinician over-rides the app's decision. Line 243-245: Review sentence – "would be" considered clinically meaningful …. Line 270: Consider omitting line 270 and incorporating line 272 into limitations. Line 24 – 247: not clear how a total of 100 patients will be sufficient – would recommend a specialist statistical review. Figures: The figure captions for figures 2 and 3 are switched. intervention vs. control. This paper was reviewed by Dr. Yvonne Bombard and her PhD student Daniel Assamad.