PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

It is estimated that up to 24% of ovarian cancers, 8-10% of breast cancers, and 3-6% of uterine cancers are hereditary in nature[1, 2]. With implications for prognosis and treatment, the National Comprehensive Cancer Network and the Society of Gynecologic Oncology recommend universal genetic testing for all women with ovarian cancer and universal screening for Lynch syndrome in all women with uterine cancer[3, 4].Additionally, these results have implications for a patient's family. In a patient with a germline pathogenic variant, first-degree relatives have a 50% chance and second-degree relatives have a 25% chance of carrying the variant.

Cascade testing describes directed genetic testing for first and second degree relatives of patients with known pathogenic genetic variants. It is well documented that despite the known importance of cascade testing for the prevention of cancer in unaffected individuals, there are several barriers to completion of cascade testing[5]. These barriers fall into two broad categories including informing at risk family members as well as family members acting upon this genetic information. Innovative models of testing, including cascade testing, was one of the recommendations made by the 2015 SGO Genetic Summit. Cascade testing for hereditary breast and ovarian cancer has also been identified by the CDC as a public health priority.

Before testing of relatives can occur, the proband (affected carrier) must disclose his or her status to family members. This process of disclosure can be difficult with barriers to disclosure including guilt, emotional distress, and complexity of genetic information, and there is evidence that while probands may discuss results with immediate family members, they will not share results with extended family, for whom the results may have consequences.[7] Currently, physicians and genetic counselors rely on the patient to inform and educate family members regarding an identified pathogenic variant. At the time of disclosure of testing results, patients are currently provided a sample hard copy letter that they can send to their family members. However, further education regarding the pathogenic variant is left completely up to the patient.

We recently completed accrual for a pilot cascade testing trial to assess the outcomes following pre- and post-implementation of a research program designed to improve disclosure and cascade testing of women identified as harboring a pathogenic variant in ovarian cancer genes. Subjects were provided three communication aids, an informational brochure, a worksheet identifying at risk family members, and a template hard copy letter to share results. Women in the study found the materials both acceptable and useful, however cascade testing rates remained disappointingly low with only 6% of first degree relatives completing cascade testing. This confirms the need to evaluate novel approaches to education and testing of relatives.

Chatbots, also known as conversation agents, are programs designed to have interactive conversations with humans. While traditionally used in sectors such as online gaming and customer service, chatbots have made their way into a number of industries including healthcare and have shown promise in areas such as managing anxiety/depression, weight loss, and medication adherence. GIA (Genetic Information Assistant) is a chatbot specifically designed as a tool for patients to use for disseminating genetic results, education, and genetic counseling resources to their family members after they themselves receive a positive result.

Patients receive a secure GIA link from their provider and then are able to send their relatives the link to GIA through texting, email, and/or Facebook messenger. Once a relative clicks on the provided link, GIA's platform is structured as a decision tree, allowing family members to construct a personalized conversation about their family member's test results. This can be done either on a smartphone or computer. GIA provides basic genetics education and risk assessment and connects family members with local genetic counseling resources to continue this conversation and/or go forward with genetic testing. At the end of the conversation, the family member has the option of having a transcript sent to them via email for their reference. The objective of the current study is to evaluate the application of GIA for cascade testing in newly identified high risk breast and gynecologic mutation carriers.

Objectives/Hypothesis

The objective of this pilot study is to evaluate the feasibility and acceptability of GIA in sharing genetic test results with family members.
To determine the utility of GIA in sharing information.
To determine the impact of GIA on downstream cascade testing rates.

Study Design: Biomedical

1. Will controls be used? No

2. What is the study design?
Prospective cohort study.

3. **Does the study involve a placebo?** No

Human Participants

Ages: 18 and older
Sex: **Female**
Race: **Any**

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. Provide target # of subjects (at all sites) needed to complete protocol.20

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites. 10% attrition rate.

3. How many subjects will be enrolled at all sites? 20

4. How many subjects will sign a consent form under this UVa protocol? **20**

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Age ≥ 18
- Undergoing genetic testing at UVA for a personal or family history of breast or gynecologic cancers in Cancer Genetics.

2. List the criteria for exclusion

- Not receiving treatment at UVA
- Not English literate
- Unable to provide consent

3. List any restrictions on use of other drugs or treatments.N/A

Statistical Considerations

1. **Is stratification/randomization involved?**No

2. What are the statistical considerations for the protocol?

Endpoints:

Determining the feasibility and acceptability of GIA in sharing genetic test results with family members will be evaluated through subject enrollment and use of the communication aid in sharing genetic results with family members. GIA allows for backstage analytics to follow objective metrics of family sharing, such as how many family members were informed, whether family members access a link, and what information family members prompted during their interaction with GIA. The utility of GIA in sharing information will be determined by collecting information about uptake and helpfulness of the aid (acceptability survey).

3. Provide a justification for the sample size used in this protocol.

This is a pilot feasibility study. Only descriptive statistics will be utilized and will be compared with historical controls.

4. What is your plan for primary variable analysis?

Enrollment number and accrual rate will determine feasibility, percentages will used to determine uptake and use, as well as utility of the communication aid.

5. What is your plan for secondary variable analysis?

Percentages will be used to determine how many family members were informed, whether family members access a link, and what information family members prompted during their interaction with GIA.

6. Have you been working with a statistician in designing this protocol? No

7. Will data from multiple sites be combined during analysis? No

Study Procedures-Biomedical Research

1. What will be done in this protocol?

1) We will approach women while at a standard of care clinic visit in the Cancer Genetics for enrollment. Participants will be consented for the study with a written consent form, after having appropriate time to read the ICF and ask questions.
2) Participants will be sent a personalized, secure, GIA link to help them communicate testing to family members should they so choose. See the ***Clear Genetics Family Sharing Process*** document.
3) Participants will be sent an electronic Acceptability Survey to send back at their convenience via email
4) We will record the following from the subject's medical record: genetic testing results, family history, clinical demographics

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.** N/A

Bibliography

1. Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proceedings of the National Academy of Sciences. 2011;108(44):18032-7.
2. Ring KL, Bruegl AS, Allen BA, Elkin EP, Singh N, Hartman A-R, et al. Germline multi-gene hereditary cancer panel testing in an unselected endometrial cancer cohort. Mod Pathol. 2016.
3. SGO Clinical Practice Statement: Screening for Lynch Syndrome in Endometrial Cancer [cited 2016 October 24]. Available from: https://www.sgo.org/clinical-practice/guidelines/screening-for-lynch-syndrome-in-endometrial-cancer/.
4. SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer [cited 2016 October 24]. Available from: https://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/

5. Menko FH, ter Stege JA, van der Kolk LE, Jeanson KN, Schats W, Moha DA, et al. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. Familial Cancer. 2018.