C4Protocol

Prospective, randomized non-inferiority trial of streamlined genetic education and testing for high-grade epithelial ovarian, fallopian and peritoneal cancer patients

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1. Background

Genetic testing in ovarian, fallopian and peritoneal cancers

Genetic testing for hereditary cancer susceptibility gene mutations is a rapidly evolving science, complicated both by an increasing awareness of its pertinence and the assumed risks associated with genetic testing and results disclosure. The demand for testing in certain populations has risen in correlation to an increasing awareness of the genetic background of several cancers. In the case of high-grade epithelial ovarian, fallopian and peritoneal cancers, up to eighteen percent of these gynecologic cancers are secondary to BRCA1 and 2 mutations, and a further five to ten percent are secondary to other associated pathogenic mutations [1,2].

Results of genetic testing may have profound implications for future family members, who can choose to undergo closer surveillance or prophylactic measures should they also carry a mutation [3]. Testing results can also impact patient treatment, as there now exist multiple FDA approved anticancer agents for BRCA mutations carriers [4-7]. For these reasons, current national guidelines, including the 2014 SGO Clinical Practice Statement and the NCCN guidelines version 2.2019 that all patients with ovarian, fallopian, or peritoneal cancer should be offered genetic testing [8,9].

The traditional model of genetic counseling

Several societies, including ASCO and the National Society of Genetics Counselors, have provided guidelines for comprehensive patient education and informed consent prior to administration of testing [10-14]. These recommendations originate from the concept that the process of counseling and testing can be psychologically detrimental to patients and their family members and are grounded in a practice of non-directive counseling [12]. Fulfillment of these recommendations has traditionally been accomplished through face-to-face consultation with a genetic counselor prior to testing.

During these consultations, patients receive approximately thirty to ninety minutes of in-depth education concerning their hereditary cancer risk and the implications of testing. This educational component of this process is exhaustively defined by ASCO's elements of informed consent for genetic counseling, which upon last update contains sixteen separate discussion topics for multi-gene panel testing [14] [Figure 1].

Figure 1:

Components of informed consent and pretest education in clinical cancer genetics [14]

Traditional Pretest Counseling for Susceptibility Testing (purpose of testing)	Pretest Counseling for Multigene Panel Testing (same general components as traditional counseling, with following special considerations)
Information on specific genetic mutation(s) or genomic variant(s) being tested, including whether range of risk associated with variant will affect medical care	Discussions of specific genes may need to be batched, because it may not be feasible to review each gene individually; high-penetrance syndromes being evaluated should be described (eg, hereditary breast-ovary, Lynch, hereditary diffuse gastric, Li-Fraumeni); patients should be aware of possible detection of high-penetrance mutations not suggested by personal or family history; genes of uncertain clinical utility may need to be described more generally
Implications of positive (mutation confirmed to be deleterious), negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result	Particular attention should be paid to implications of positive results in less well-understood or lesser-penetrance genes and in findings of mutations in genes associated with syndromes not suggested by personal or family history
Possibility test will not be informative	Attention should be paid to current high rate of variants of uncertain significance
Risk that children and/or other family members may have inherited genetic condition	Highlight potential reproductive implications to family of mutations in genes linked to recessive disorders (eg, *ATM*, Fanconi's [*BRCA2*, *PALB2*], *NBN*, *BLM*)
Fees involved in testing and counseling; for DTC testing, whether counselor is employed by testing company	
Psychological implications of test results (benefits and risks)	
Risks and protections against genetic discrimination by employers or insurers	
Confidentiality issues, including DTC testing companies and policies related to privacy and data security	
Possible use of DNA samples for future research	
Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing	
Importance of sharing genetic and genomic test results with at-risk relatives so they may benefit from this information	
Plans for disclosing test results and providing follow-up	

Abbreviation: DTC, direct to consumer.

*Changes from the 2010 version include the discussion of multigene panel result management, discussion of batched genes rather than individual genes and acknowledgement of uncertain results and the high rate of VUS in multigene panel results.

The critical components of the genetic counseling process include a medical and family history evaluation, cancer risk assessment, genetic education, discussion of testing, and arrangement of follow-up.

Failure of the traditional model in ovarian, fallopian and peritoneal cancer patients

Dependence on this model in the setting of universal testing recommendation, however, has several flaws. The mutation rate is high enough and the implications of a positive mutation great enough to tip the risk and benefit ratio clearly to the side of testing. Thus, genetic counseling for the ovarian cancer population has undergone an

implicit shift from non-directive to directive. While the full ASCO pre-test counseling guidelines may still be appropriate in certain populations for whom universal testing has not been recommended by multiple professional societies, it seems reasonable to expedite the process for ovarian cancer patients.

Second, the lack of consistent referral and limited supply of counselors associated with the traditional model, when combined with non-directive counseling, has resulted in a persistent failure to achieve universal testing, with approximately 25% of patients receiving BRCA1 and 2 testing [15,16]. The supply and demand issue will likely worsen, as genetic testing referrals for other solid tumors are also increasing in frequency. In short, the recommendation for universal BRCA1/2 testing in patients with high-grade epithelial ovarian, fallopian or peritoneal carcinoma has created a need for an alternate education and testing process.

Alternative models of service delivery

Several alternative models have been suggested, including group counseling, teleconferencing, telephone counseling and post-test counseling only [17,18]. More recently, the streamlined model has been successfully incorporated into several institutions through quality improvement initiatives [19,20]. In this model, the patients are counseled and testing at their primary oncologic appointment, either by the providers themselves or by embedded genetic counselors. These modifications have been shown to be easily implemented and to increase the institutions' counseling and testing rates by significant margins.

Safety of alternative models

While expedited models may increase efficiency and genetic testing uptake, it must be established that these methods are not detrimental to patients. ASCO and NSGC's original policies regarding pre-test education originate from an effort to minimize patient distress. As reported in its policy statement on genetic counseling for cancer susceptibility mutations in 2003, "a definitive genetic test may have considerable medical and psychological implications," and its counseling framework intends to prepare the patient for these [12].

This assumption may not hold true, however, in the setting of more directive counseling, when the stakes for patients and family members are more significant. A

positive BRCA 1 or 2 result, logically, has been shown to have at least a temporary impact on psychological well-being, but this is present even after traditional pre-test counseling [21]. Multiple studies, however, have demonstrated that BRCA 1 and 2 testing in high-risk populations does not generally increase patient distress [22,23]. Furthermore, the use of certain alternate models to provide pre-test education, such as telephone counseling and teleconferencing, did not increase patient distress when compared to the traditional model [17,24]. Unfortunately, uptake of testing via telephone counseling was shown to be lower than that achieved by the traditional method in a prospective non-inferiority trial [17], and videoconferencing still requires possible over-utilization of genetic counselors in a pre-test setting.

Purpose of study

As evidenced by this discussion, a model that achieves the goal of increasing uptake and decreasing resource utilization while not significantly increasing patient distress has yet to be established. We hypothesize that a streamlined model of service delivery will not have a detrimental effect on patient distress with the counseling and testing process. We also hypothesize that this model will adhere to near-universal testing uptake without increasing cost burden on the healthcare system. This would be the first randomized trial to investigate the safety and non-inferiority of this promising new genetic service delivery model, providing an alternate, resource-effective method of pre-test education that could improve genetic testing uptake without increasing adverse psychological effects.

2. Study Objectives

Primary Objective

a. To determine if implementation of a streamlined model of genetic service delivery increases patient distress as measured by the Multidimensional Impact of Cancer Risk Assessment Scale when compared to the traditional model of counseling [25].

Hypothesis: An expedited education and testing model in this patient population will not decrease patient satisfaction with genetic counseling or increase patient anxiety.

Secondary Objectives

a. To compare cost between the traditional genetic counseling model and the streamlined model.

Hypothesis: An expedited education and testing model in this patient population will be less expensive compared to the traditional model.

b. To compare genetic testing uptake between the streamlined and traditional models.

Hypothesis: In this study setting, both groups will have close to universal testing uptake.

c. To observe differences in distress throughout the genetic education and testing process, including pre-education, post-education, and post-results disclosure.

Hypothesis: The process of genetic education, testing and results review causes minimal distress in patients.

3. Study Design

3.1 Experimental Design

This is a prospective, randomized non-inferiority trial.

3.2 Study location

This study will recruit from the gynecologic oncology clinics at Duke Cancer Institute and collaborating institutions.

3.3 Study time period

Estimated ascertainment completion date: 12/31/2020

Estimated study completion date: 3/31/2021

3.4 Study population

The study will recruit from the gynecologic oncology clinic at Duke Cancer Institute and collaborating institutions. A maximum of 112 patients will be consented.

4. Study Procedure

4.1 Subject Selection and Enrollment

4.1.2 Inclusion and Exclusion Criteria

Inclusion:

- Age greater than 18 years
- Female
- Either a) pathologically confirmed diagnosis of high-grade epithelial ovarian, fallopian or peritoneal cancer via biopsy or surgical pathology or b) cytologic diagnosis consistent with high-grade epithelial ovarian cancer.
- Presenting to Duke gynecologic oncology clinic or collaborating institution for first outpatient visit following pathologic or cytologic diagnosis. If logistic constraints prevent the patient from being enrolled at her initial visit, she will be eligible for enrollment up to initiation of her fourth cycle of chemotherapy.

Exclusion:

- Known family or personal history of an inherited cancer susceptibility mutation
- Previously received genetic counseling or testing for an inherited cancer susceptibility mutation
- Insurance provided by an insurance company that requires face-to-face genetic consultation prior to testing
- Unable to read or speak English as study design includes video assisted educational materials in English
- Blind or deaf as study design includes video assisted educational materials in English

4.1.3 Recruitment Procedures

Recruitment

- Recruitment will occur in the gynecologic oncology clinics at Duke Cancer Institute and collaborating institutions.
- Potential subjects will be identified by the primary research coordinator prior to their clinic visit and will be flagged for the primary provider, fellows, residents and APPs to make their potential eligibility for the trial known.

Eligibility Determination and Introduction of Trial

- Once the patient arrives in clinic, both the research coordinator and primary provider will review her eligibility for the trial based on the above stated criteria.
- If eligible, either the primary research coordinator or provider will give a brief explanation of the trial and assess patient's willingness to enroll.
- If the patient agrees to enroll, the process of consent will begin. If the patient does not agree to enroll, a note stating that the patient was approached and then declined enrollment will be placed in the EMR so that she is not approached again. The patient's basic demographic information will also be recorded in the secure online database for later comparison of demographic information between those who were amenable to alternative forms of service delivery and those who did not wish to participate.

4.2 Process of Consent

4.2.1 Consent Process

- If the patient is amenable to enrollment, she will be consented in one of the clinic rooms in the gynecologic oncology clinic during her primary appointment by either the clinical research coordinator or her primary provider.
- The IRB approved consent will be reviewed in full, including trial purpose, stated objectives, study procedures, risks, benefits, and costs. The consent process will take place in a clinic exam room with a closed door to ensure privacy.
- Patients will have ample time while in clinic to ask questions of the research coordinator or gynecologic oncology provider. Up to thirty minutes will be allotted for review of consent form. If they have questions after their consent is signed, the contact information of the primary investigator will be listed in the consent form.

Subjects will be emailed a copy of the consent form once it is signed. If they do not have an active email account, a paper copy with their signature will be printed for them after they have signed the consent.

4.2.2 Legal Capacity to Give Consent

- The subject must have full capacity to consent.

4.3 Risk and Benefit Assessment

4.3.1 *Risk*

- The first risk associated with this proposed study includes the use of secure medical records. To ensure that patient confidentiality is maintained, all data retrieval will be performed by the principal investigator or assigned researchers using password-secured computers. Each subject will be assigned a subject ID code that will be linked to the medical record number. This will be generated using REDCap database and will be stored on a standalone database server hosted by Duke Health Technology Services (DHTS) and will only be accessible to the key personnel of this study. Collaborating sites will share the same Duke REDCap.
- Risks of genetic testing will also be associated with the study, as a majority of patients in both arms will likely undergo testing. However, this is a risk associated with a separate, well-established standard of care in this population rather than with the study intervention. Thus, while it will be addressed with the patient when they complete their separate, standard consent for genetic testing, it is not considered to be an incremental risk of this study.
- The study also incurs a potential incremental risk of adverse psychological reactions to streamlined genetic counseling and testing. Our hypothesis is that the streamlined model will not significantly increase patient distress with the genetic counseling and testing process.

4.3.2 *Benefit*

- Patients will receive genetic risk assessment, which is currently recommended for everyone in this patient population. There is no other direct benefit provided to

subjects included in this study. However, we hope that the findings of this study will lead to increase analysis and uptake of expedited models of genetic education and testing, thus potentially benefiting this patient population and their family members.

4.3.3 *Cost*

Charge of testing and face-to-face post-test counseling will be billed as per usual. The only incremental cost incurred by the participant will be the time spent participating in trial activities. Traditional pre-test counseling is not currently billed at Duke Cancer Institute, nor would the streamline education process be.

4.3.4 Compensation

- No compensation will be provided for participation in this trial.

5. Study Design

5.1 Randomization

Following consent, the clinical research coordinator will randomize the patient to either the Traditional Group (TG) or Streamlined Group (SG). The randomization process will have occurred previously using the REDCap randomization tool.

5.2 Study Procedures (See Figure One)

5.2.1 *Baseline Questionnaires (Both Groups)*

- After randomization, each subject will complete a series of baselines questionnaires on a tablet in the gynecologic oncology clinic, entering their results directly into the secure REDCap database. These baseline questionnaires include a basic numeracy test, the baseline anxiety and distress survey (IES) and the demographic information questionnaire, which will include questions concerning age, race, marital status, home address, and income [26,27].

5.2.2 *Tradition Counseling Group (TG)*

a. Formal Consultation Scheduling

- After completion of baseline surveys, the TG subjects will be referred to a formal pre-test consultation with a genetic counselor that will be scheduled for a date approximately 2-4 weeks after their primary appointment (for patients in whom results will determine treatment, appointments will likely be expedited). They will be made aware of the date and time of this appointment prior to leaving their initial visit.

b. Electronic Family History Questionnaire

- TG subjects will complete an electronic family history questionnaire (FHQ) within one week of the primary visit. This is a system already employed by the Duke Clinical Genetics Department. An email is sent to the subject's primary email account with a link to a secure, HIPAA compliant portal, in which the subject can then enter her family cancer history.
- A member of the genetics team will curate the results by contacting the subject to review common errors and clarify any ambiguities in the pedigree.

c. Formal Consultation and Post-Counseling Distress Survey

- The TG subjects will then meet with the genetic counselor at the previously scheduled appointment time. During this visit, they will receive approximately thirty to sixty minutes of counseling regarding genetic testing and potential results. The discussion is based on the ASCO and NCCN guidelines of informed consent for genetic testing.
- After counseling, participants will be given the option to undergo a multi-gene panel genetic test either via saliva or blood sample. Those who agree to testing will also complete the standard genetic testing consent form. As per standard practice of the clinical genetic service at DCI, patients will also be asked to provide consent for somatic tumor testing of surgical specimen (non-cytologic).
- Subjects will complete a post-education distress and anxiety survey (IES) via an email link to a confidential REDCap survey link within one week of formal consultation.

5.2.3 *Streamlined Group (SG)*

a. Video-Assisted Genetic Education

- After completion of the baseline surveys, the SG subjects will watch an approximately eight minute long genetics education video. This video will be made with the assistance of Duke University genetic counselors and gynecologic oncology providers. It will consist of a discussion of genes and mutations, the recommendation of universal testing for high grade epithelial ovarian cancer, a review of genes associated with ovarian cancer predisposition, the possibility of uncertain results including variants of undetermined significance, the potential for undetected mutations in known or unknown cancer susceptibility genes, the potential impact on personal treatment and on family members, the possibility of genetic discrimination and the legal protection of genetic information.
- After watching the video, the primary oncologic provider will then offer multi-gene panel testing.
- All subjects will then have the option to "opt out" and receive formal genetic counseling prior to making a decision about testing.
- If the subject elects to undergo genetic testing, she will fill out the standard genetic testing consent form. As per standard practice of the clinical genetic service at DCI, patients will also be asked to provide consent for somatic tumor testing of surgical specimen (non-cytologic).

b. Electronic Family History Questionnaire

- SG subjects will complete an electronic family history questionnaire (FHQ) within one week of the primary visit. This is a system already employed by the Duke Clinical Genetics Department. An email is sent to the subject's primary email account with a link to a secure, HIPAA compliant portal, in which the subject can then enter her family cancer history.
- A member of the genetics team will curate the results by contacting the subject to review common errors and clarify any ambiguities in the pedigree.

c. Post-education distress measurement

- Subjects will complete a post-education distress and anxiety survey (IES) via an email link to a confidential REDCap survey link within one week of formal consultation.

5.2.3 Results Disclosure (Both groups)

- Subjects will be notified of their results by the genetic counselor over the phone and triaged accordingly.
    - Deleterious mutation, VUS or high-risk family history despite negative genetic testing results: Scheduled for formal post-testing consultation 2-4 weeks after result return
    - No deleterious mutation or VUS identified on genetic testing and low risk family history: No further genetics follow-up needed

5.2.4 Follow-up

- All subjects will take a satisfaction with genetic counseling survey (MICRA) after receiving results approximately seven days after either formal consultation or reception of results over the phone [25]. The survey will be sent via email via a confidential REDCap survey link.

5.3 Outcome Variables

5.3.1 Demographic information

Measurement time: Baseline

Description: Demographic information, including cancer history, age, race, marital status, and income will be collected from each participant upon enrollment.

5.3.2 Numeracy assessment

Measurement time: Baseline

Description: Numeracy and health literacy will be assessed using the Newest Vital Sign survey, a six-question survey that asks questions about a provided ice cream nutrition label [26].

5.3.3 Electronic family history

Measurement time: A secure email sent to patient immediately after first visit; completed at home within one week of visit

Description: This is a system already employed by the Duke Clinical Genetics Department. An email is sent to the subject's primary email account with a link to a secure, HIPAA compliant portal, in which the subject can then enter her family cancer history for three generations. A member of the genetics team will curate these results.

5.3.4 Anxiety and depression

Measurement time: Baseline, post-education and post-results disclosure

Description: The Impact of Events Scale (IES) has been used widely as a means of measuring patient distress (particularly intrusive thoughts or avoidance) over a defined incident [27]. This evaluation will be used to identify trends in anxiety or depression in both arms throughout the education and testing process. In this trial, the "incident" will be described as "the risk of my cancer being hereditary."

5.3.5 Distress

Measurement time: Post-results disclosure

Description: The multidimensional impact of cancer risk assessment questionnaire (MICRA) is a 25-question validated tool that measures the impact of result disclosure in patients, particularly markers of distress [25].

5.3.6 Resource utilization

We will evaluate the cost of physician, genetic counselor and genetic assistant time based on average base wages for these positions and total mean time spent by each of these providers. These estimates will be obtained for approximately forty patients –twenty from each arm – enrolled mid-trial to ensure that the process time in the streamlined group has reached full efficiency. Each provider will record time for each of these parameters using a stopwatch, with total times entered into the REDCap database. Times measured in both arms will include:

Family History Curation

GC phone time

GC documentation or computer entry

Staff phone time

Staff documentation or computer entry

Pre test counseling (Any time prior to results disclosure)

GC phone time

GC documentation or computer entry

GC face-to-face counseling

Staff phone time

Staff documentation or computer entry

Post test (From time of results disclosure on)

GC results disclosure phone time

GC face-to-face counseling

GC other phone time (not including results disclosure)

GC documentation or computer entry

Staff phone time

Staff documentation or computer entry

We will evaluate the cost of physician, genetic counselor and genetic assistant time based on average base wages for these positions and total mean time spent by each of these providers.

5.4 Statistical Methods

5.4.1 Demographic and Baseline Survey Information

The SG and TG will be compared at baseline regarding demographic information, medical and family history and baseline distress as measured by the Impact of Events Scale. Categorical variables will be tested using the Chi-Square test. Continuous variables will be assessed using the Student T test or the Mann-Whitney U test for non-normal data. Equality of variance across these variables will be assessed. Any variables with a significant difference greater than p=0.1 will be controlled for in future analyses.

5.4.2 Primary endpoint

The study is powered as a non-inferiority analysis of distress associated with streamlined genetic education and testing versus traditional pre-test genetic counseling and testing.

A two sample one-sided t-test is used to check the non-inferiority for the experimental treatment in terms of the MICRA (Multidimensional Cancer Risk Assessment questionnaire). We assumed the mean MICRA scores for both experimental arm and control arm will be the same and equal to 13.5, with a common standard deviation of 8.4. These values were obtained from a study that assessed the MICRA in a similar patient population [25]. Using these estimates, a total sample size of 102 (51 patients each arm) will provide 80% power to detect the non-inferiority for the experimental treatment with a significance level of 0.05 and a non-inferiority margin of 4.2 (50% standard deviation). This margin was chosen as a high general MICRA score has previously been considered to be one standard of deviation above the mean; thus, we are taking a more conservative approach by using a non-inferiority margin of 0.5 the expected standard deviation observed in Cella et al [28]. When incorporating a potential 10% attrition rate, the total sample size will be 112.

5.4.3 Secondary endpoints

Resource utilization

Mean resource utilization will also be compared between the two models using summary statistics.

Genetic testing uptake

Genetic testing uptake between the two groups will be compared using logistic regression.

5.4.4 Exploratory endpoints

Impact of Events Scale

Mean changes in the Impact of Events Scale scores between each administration point will be compared between the two arms using the Wilcoxon rank sums test.

5.5 Data and Safety Monitoring

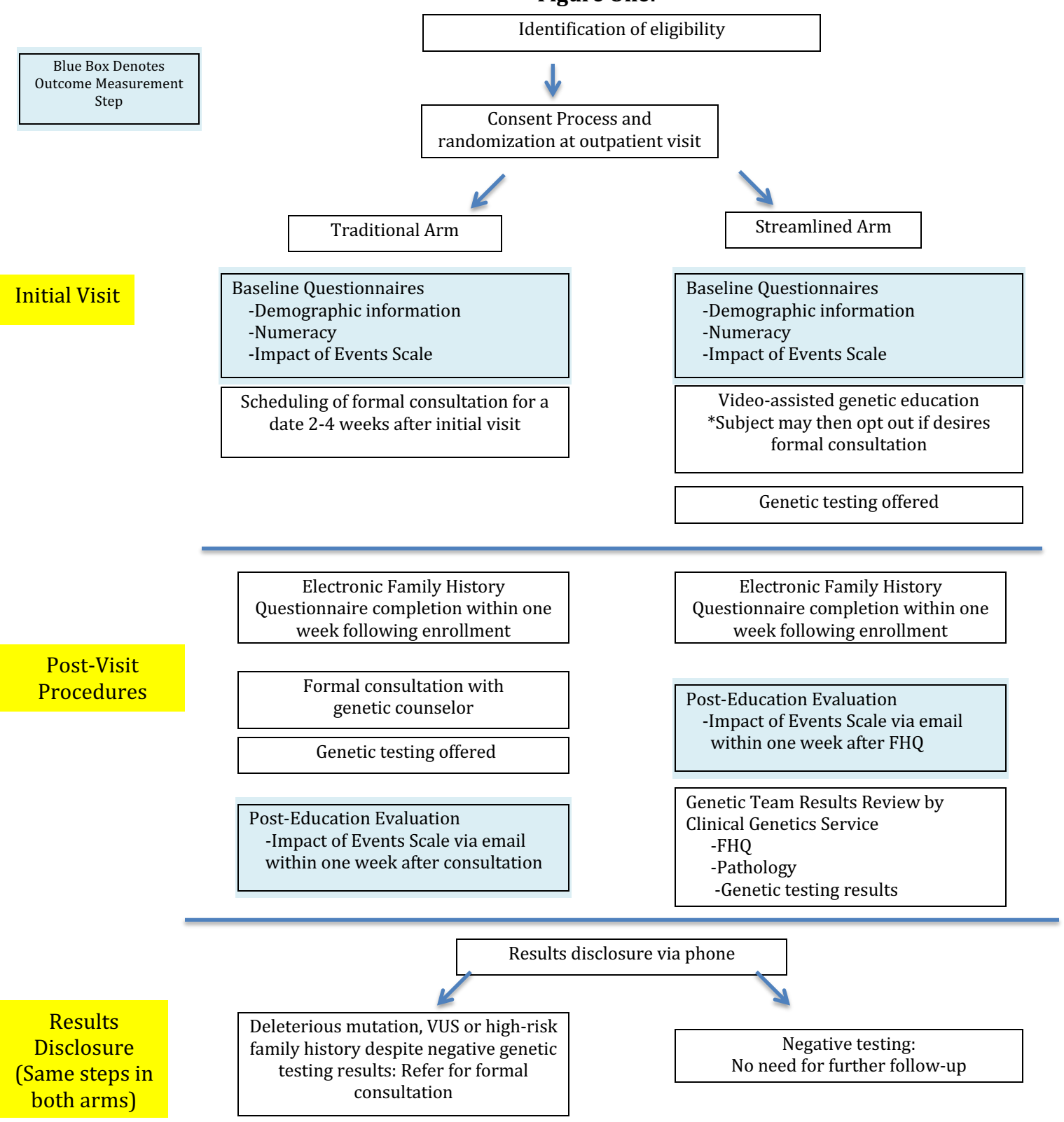
Subject safety will be maintained through use of only secure computers and networks for data collection and storage. Subjects will be assigned a new identifying number for

database organization purposes that will in no way be associated with any subject identifiers. The code list containing each subject's new assigned number will be stored in RedCap database and on a standalone database server, hosted by Duke Health Technology Services (DHTS).

5.6 The Role of External Personnel

No external personnel will be involved in this study.

Figure One:


Blue Box Denotes Outcome Measurement Step
Identification of eligibility
Consent Process and randomization at outpatient visit
Traditional Arm
Streamlined Arm
Initial Visit
Baseline Questionnaires
-Demographic information
-Numeracy
-Impact of Events Scale
Scheduling of formal consultation for a date 2-4 weeks after initial visit
Baseline Questionnaires
-Demographic information
-Numeracy
-Impact of Events Scale
Video-assisted genetic education
*Subject may then opt out if desires formal consultation
Genetic testing offered
Post-Visit Procedures
Electronic Family History Questionnaire completion within one week following enrollment
Formal consultation with genetic counselor
Genetic testing offered
Post-Education Evaluation
-Impact of Events Scale via email within one week after consultation
Electronic Family History Questionnaire completion within one week following enrollment
Post-Education Evaluation
-Impact of Events Scale via email within one week after FHQ
Genetic Team Results Review by Clinical Genetics Service
-FHQ
-Pathology
-Genetic testing results
Results Disclosure (Same steps in both arms)
Results disclosure via phone
Deleterious mutation, VUS or high-risk family history despite negative genetic testing results: Refer for formal consultation
Negative testing:
No need for further follow-up

Post-Results Evaluation completed within 1 week after consultation -Impact of Events Scale -MICRA	Post-Results Evaluation sent via email within 1 week after phone call -Impact of Events Scale -MICRA

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