PROTOCOL TITLE: Use of a computerized decision aid for prenatal aneuploidy screening

Short Title: Aneuploidy decision aid

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
MSSKQ	Maternal serum screening knowledge questionnaire
cfDNA	Cell-free DNA screening

PROTOCOL SYNOPSIS

Study Title	Use of a Computerized Decision Aid for Prenatal Aneuploidy Screening
Funder	• National Center for Advancing Translational Sciences (NCATS), NIH, Grant #UL1TR001111 • UNC Department of OBGYN Cefalo-Bowes Grant (internal funding)
Clinical Phase	Phase II
Study Rationale	• All women should be offered aneuploidy screening or testing in each pregnancy • Screening and testing options are complex • Decision aids have been shown to improve knowledge and decrease decisional conflict with healthcare decisions, including aneuploidy screening • Prior decision aids which have been evaluated for aneuploidy screening did not include the newest screening option of cell-free DNA
Study Objective(s)	Primary • To evaluate whether use of the computerized decision aid is noninferior than an abbreviated visit with a genetic counselor in increasing patient knowledge Secondary • To evaluate whether use of the computerized decision aid is noninferior than an abbreviated visit with a genetic counselor in

	decreasing patient decisional conflict • To evaluate whether use of the decision aid in addition to genetic counseling improves patient knowledge and decisional conflict over genetic counseling alone • To examine test chosen for aneuploidy screening
Test Article(s) *(If Applicable)*	A computerized decision aid was developed within a tablet-based application, available in Spanish and English, at a 10th grade reading level, to aid in patient education surrounding aneuploidy screening and testing options
Study Design	Unmasked randomized controlled trial
Subject Population **key criteria for Inclusion and Exclusion:**	Inclusion Criteria • English and Spanish-speaking pregnant women • Undergoing genetic counseling for indication of aneuploidy screening • Ages 18-50 Exclusion Criteria 1. Multiple gestation 2. Prior aneuploidy screening in current pregnancy 3. Prior abnormal ultrasound in current pregnancy
Number Of Subjects	200
Study Duration	Each subject's participation will last for the duration of the study visit (approximately 45 minutes).

	The entire study is expected to last 12 months.
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: Women scheduled for genetic counseling for indication of aneuploidy screening will be approached regarding eligibility and willingness to participate prior to their scheduled appointment. (2) Intervention: Participants will be randomized either to use the above-described decision aid prior to genetic counseling or to genetic counseling alone. (3) Follow-up: None after study visit
Efficacy Evaluations	(1) Knowledge: A 12 question modification of the MSSKQ questionnaire will be used to assess knowledge (2) Decisional conflict: A validated low-literacy decisional conflict scale will be used to assess decisional conflict
Pharmacokinetic Evaluations	N/A
Safety Evaluations	N/A
Statistical And Analytic Plan	(1) Primary outcome: Noninferiority of knowledge will be assessed graphically and with Wilcoxon Rank-Sum (2) Secondary outcomes: knowledge and decisional conflict scores will be assessed with Wilcoxon Rank-Sum
DATA AND SAFETY MONITORING PLAN	Participants were provided with contact information for the PI should they have any concerns. No safety concerns are anticipated.

1 BACKGROUND AND RATIONALE

Many different aneuploidy screening and diagnostic testing options are available to patients based on gestational age, all with different risks and benefits. Cell-free DNA screening has improved sensitivity and specificity for common aneuploidies[1] but likely reduced detection of other chromosomal abnormalities.[2] However, traditional screening such as first trimester screening, which have poorer detection characteristics for common aneuploidies, may be more likely to identify pregnancies other, less common, chromosomal abnormalities.[2] Diagnostic testing choices include chorionic villus sampling and amniocentesis, both of which carry a low risk of pregnancy loss of approximately 1 in 455 to 1 in 900 respectively.[3] Counseling on screening and testing options is recommended by the American College of Obstetrics and Gynecology for all women, ideally at the first prenatal visit.[4] Additionally, recommendations by the American College of Medical Genetics emphasize the importance of appropriate pretest counseling for patients undergoing prenatal screening with cell-free DNA.[5]

This increasing number of screening modalities complicates prenatal counseling for prenatal care providers and can be difficult for patients to understand, especially patients with low health literacy.[6] While many patients may be aware of trisomy 21, many have never heard of other aneuploidies and may be unfamiliar with the basic principles of genetic screening and prenatal aneuploidy detection.

Because low health literacy affects many women of reproductive age and because most obstetric providers have limited time in an initial prenatal visit to explain the rapidly expanding choice of tests, our aim was to develop a decision aid for aneuploidy screening and testing that could easily be used in various clinics and settings. Decision aids have been shown to improve patients' knowledge and decrease decisional conflict with health care decisions in healthcare settings,[6] and in the field of obstetrics and gynecology.[6,7] This is particularly true when decisions are complex and involve patient value assessment.[6] A decision aid has been previously developed and tested to address aneuploidy screening,[8] though an important new screening modality in cell-free DNA has become available since the development of this tool. We hypothesize that a computerized decision aid to review available aneuploidy screening and testing options would not be inferior to a counseling visit with a genetic counselor in increasing patient knowledge. The combination of the decision aid followed by a genetic counseling appointment would also be expected to decrease decisional conflict.

1.1 Description of Intervention

A decision aid incorporating all aneuploidy screening and diagnostic testing options available at the time of the study was developed with input from maternal fetal medicine physicians, a geneticist, and genetic counselors. This was designed within a tablet-based application. The decision aid was also translated into Spanish by a single translator and the translation reviewed by a second native Spanish speaker. The language was simplified to a 10^{th} grade reading level on the Flesch-Kincaid scale. Completion of the decision aid takes approximately 20 minutes. Information surrounding patient age and gestational age are incorporated to guide the study participant toward available options.

2 STUDY OBJECTIVE

2.1 Primary Objective

The primary hypothesis of this study was that knowledge scores of women in group 2 following completion of the decision aid only would not be inferior to knowledge scores of women in group 1 following genetic counseling. A noninferiority limit of 1 question different on a 12 point questionnaire was selected as a clinically relevant difference.

2.2 Secondary Objective

Secondary outcomes included decisional conflict following decision aid completion, decisional conflict following decision aid completion and genetic counseling, change in knowledge score after genetic counseling in women who used the decision aid, choice of testing, and pursuit of invasive testing with high risk results.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an unblended randomized controlled trial.

Women randomized to group 1 will meet with the genetic counselor as scheduled, then complete the knowledge and decisional conflict assessments. Women randomized to group 2 will self-administer the decision aid within the app, then complete the knowledge and decisional conflict assessments. Following this, they will met with the genetic counselor as scheduled; following this appointment, they will again complete the same assessment. Additionally, prior to and following meeting with the genetic counselor, women in group 2 will be asked whether they would or did find it helpful to meet with a genetic counselor.

Genetic counselors will be educated prior to study initiation that their counseling should not be modified based on group assignment; generally, women < 35 years old received abbreviated counseling on aneuploidy screening and testing options and those ≥ 35 years old received more extensive counseling. Within ACMG guidelines, all screening tests are available to all women; cost information and insurance coverage information on available tests will also be provided prior to final decision making. Women will then undergo their screening or testing modality of choice. All study participation and completion of initial screening will be completed within the single encounter.

3.2 Allocation to Treatment Groups and Blinding (if applicable)

Via a coin-flip algorithm within the decision aid application, women will be randomly assigned to group 1 (control group) or group 2 (decision aid group)

3.3 Study Duration, Enrollment and Number of Subjects

Study duration for each participant is limited to the single study visit during which patients are enrolled, complete questionnaires, and complete genetic counseling. 200 participants will be enrolled. This is anticipated to take approximately 12 months.

3.4 Study Population

English and Spanish-speaking women with a singleton gestation at less than 22 weeks who are scheduled to meet with a genetic counselor at one of three prenatal diagnosis clinics for a discussion of aneuploidy screening and testing options are eligible for participation.

Exclusion criteria include: multiple gestations, prior abnormal ultrasound in the current pregnancy, or prior aneuploidy screening in the current pregnancy.

4 STUDY PROCEDURES

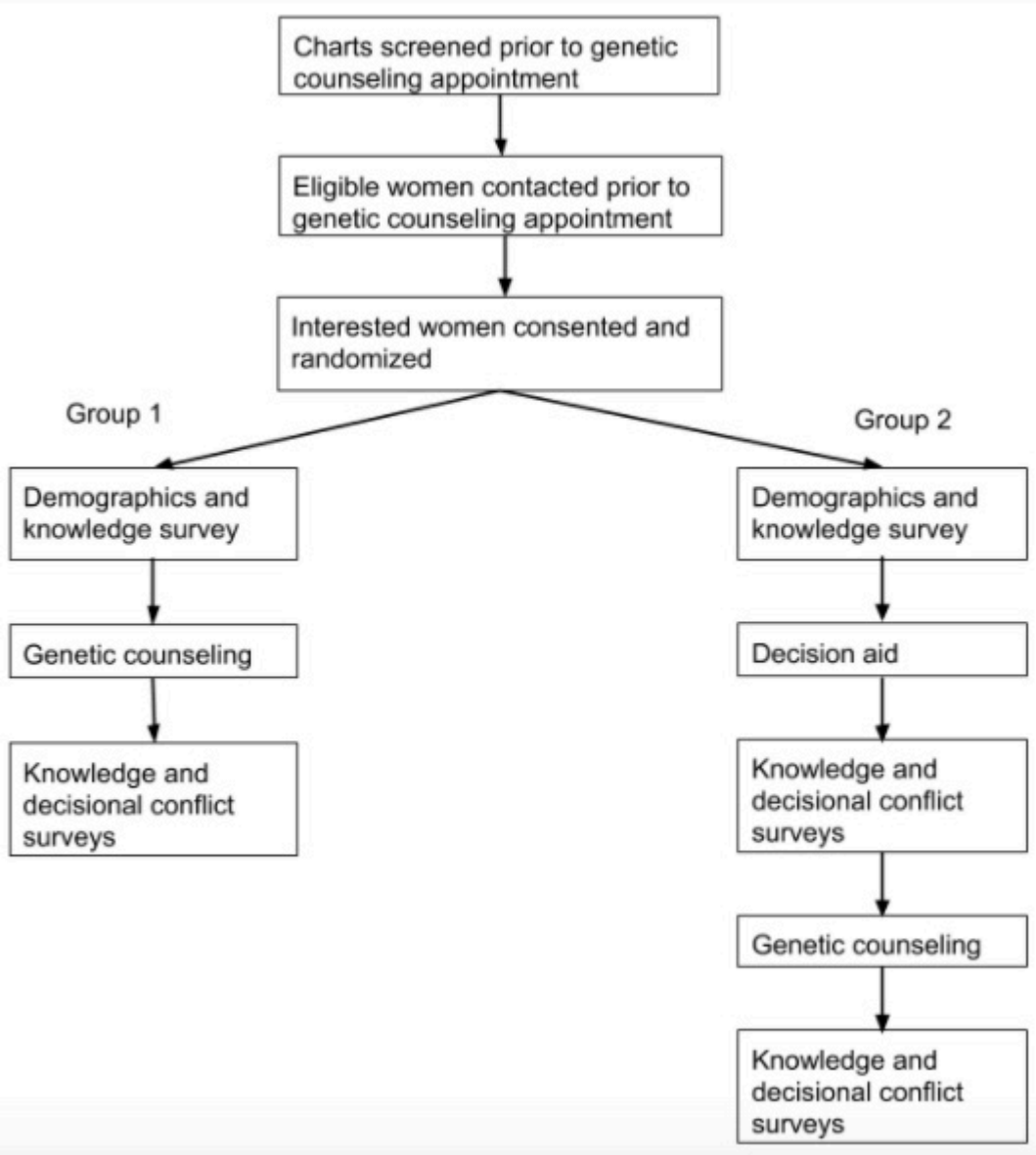
4.1 Screening procedure

For the randomized trial, charts of women scheduled to see a genetic counselor for a discussion of aneuploidy screening or testing were screened for eligibility and eligible women were contacted within a week before their visit by telephone by trained study personnel. Women who indicated in the medical record that they preferred Spanish were contacted by Spanish-speaking study personnel. Those who agreed to participate were asked to arrive early for their appointment to be enrolled in the study.

4.2 Intervention

Following informed consent, the app was accessed and a study ID assigned. Via a coin-flip algorithm within the app, women were randomly assigned to group 1 (control group) or group 2 (decision aid group). As it was not pragmatic for this study, randomization assignment was not blinded. Investigators were not involved in developing the randomization scheme within the app. All women completed an initial demographic and knowledge questionnaire immediately following randomization via self-administered assessments within the app.

Study flow is described in the below figure. Women randomized to group 1 met with the genetic counselor as scheduled, then completed the knowledge and decisional conflict assessments. Women randomized to group 2 self-administered the decision aid within the app, then completed the knowledge and decisional conflict assessments. Following this, they met with the genetic counselor as scheduled; following this appointment, they again completed the same assessment. Additionally, prior to and following meeting with the genetic counselor, women in group 2 were asked whether they would or did find it helpful to meet with a genetic counselor.



4.3 Subject Completion/ Withdrawal procedures

Participants are instructed to inform their enrolling research study personnel should they desire to withdraw and participation could be terminated at that time.

5 STUDY EVALUATIONS AND MEASUREMENTS (how measurements will be made)

- Demographic characteristics will be abstracted from questionnaires and medical chart
    - Age
    - Race/ethnicity
    - Preferred language
    - Parity
    - Gestational age
    - Site of enrollment
    - Insurance status
    - Employment status
    - Education level
    - History of genetic counseling in prior pregnancy
- Baseline knowledge assessment
    - This will be assessed via the previously described modified MSSKQ questionnaire prior to intervention
- Knowledge and decisional conflict scores as described will be collected via self-administered questionnaires embedded within the application

6 STATISTICAL CONSIDERATION

6.1 Sample size calculation

An initial power calculation was performed using historical data from the maternal serum screening questionnaire assuming a standard deviation of 3 questions; to achieve 80% power with a 2-tailed alpha of 0.05, 92 women would be needed in each arm. Assuming a 7.5% fall-out rate from women with nonviable pregnancies, 100 patients were required in each arm for a total enrollment of 200 women.

6.2 Statistical Methods

Baseline demographics

- Mean age - Wilcoxon rank sum
- AMA as categorical variable - chi2
- Race/ethnicity - Fisher exact
- Mean GA - Wilcoxon rank sum
- GA<14 wks as categorical - chi2
- Insurance status - Fisher exact
- Employed yes/no - chi2
- Education level - fisher exact
- Religion - Fisher exact
- Prior GC - chi2
- Planning invasive testing - Fishers exact
- Mean knowledge score on enrollment - Wilcoxon rank sum

Results

1. Compare control group following genetic counseling to intervention group following decision aid
    - Mean knowledge - Wilcoxon rank sum
    - Mean decisional conflict - Wilcoxon rank sum
    - Planned test - Fisher exact

2. Compare control group following genetic counseling to intervention group following decision aid and genetic counseling
    - Mean knowledge - Wilcoxon rank sum
        1. Represented in figure
    - Decisional conflict - Wilcoxon rank sum
        1. Represented in figure
    - Planned test - Fisher exact
3. Compare intervention group following decision aid to intervention group following both decision aid and genetic counseling
    - Mean knowledge - Wilcoxon signed rank
        1. Represented in figure
    - Decisional conflict - Wilcoxon signed rank
        1. Represented in figure
    - Planned test - descriptive (% changed)

No interim analyses are planned.

7 DATA COLLECTION AND MANAGMENT

Results to questionnaires are stored within the study application and will be downloaded onto a secure server by study personnel following each study visit. These files will be encrypted and password protected. This data will then be transferred into REDCap data management system for storage and access for statistical analysis by the primary investigator.

8 REFERENCES

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