IRB #17-987
PROTOCOL
Protocol Continuing Renewal

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** Due to site based permission to restart research efforts, we are reinstating some in-person recruitment and survey distribution procedures both at CCF and MetroHealth locations. CCF IRB is the IRB of Record for this study at both CCF and MetroHealth sites. - see highlighted sections

Introduction

Noninvasive prenatal genetic testing (NIPT) is an important new screening test option provided to pregnant women in the first trimester of pregnancy. The advantage of this screen is that it provides information about the risk of trisomy 13, trisomy 18, and trisomy 21 with greater accuracy than conventional screens. At the same time, NIPT can produce information about the risk of a cohort of other fetal genetic variants, including sex chromosome aneuploidies and microdeletion syndromes. While not yet clinically recommended for whole exome sequencing, the potential for this next clinical application already exists. The challenge is that, while this is an important new test, there is little data about how to best structure patient-centered decisions about its use, including the decision to use this screen or not and how the information may directly inform subsequent prenatal care decisions. The purpose of this study is to gain formative data about current practice patterns with respect to how NIPT is discussed in the clinical visit and to use this data to help inform best practices for its continued use in the clinical setting.

Background and Significance

Noninvasive prenatal genetic testing (NIPT), also known as cell-free fetal DNA screening, has dramatically altered the delivery of prenatal care. Prior to NIPT, fetal aneuploidy risk was assessed using conventional screens, most commonly maternal serum screens (MSS, e.g. the Quadruple screen). While MSS provided information about the risk of trisomy (T) 21, T13, and T18, its use led to many false positive results which required amniocentesis or chorionic villus sampling to clarify. The risk of iatrogenic miscarriage from these diagnostic procedures is low, but the possibility of this consequence is a major driver in how healthcare providers and patients think about prenatal genetic risk and assessment. NIPT has significantly changed this long-standing paradigm. While not diagnostic, NIPT offers increased accuracy with lower false positive and false negative rates than MSS when screening for common autosomal aneu-ploidies. Unlike conventional screens, NIPT provides information never before a part of routine screening, such as the presence of sex chromosome aneuploidies (SCAs), microdeletions, and fetal sex. Already the capability exists to utilize NIPT in conjunction with whole exome sequencing to detect an unlimited number of fetal genomic variants, many with undetermined significance. The list of conditions that NIPT can screen for is expanding rapidly and has

outpaced the rate at which evidence-based strategies for its integration can be developed and implemented.

Expectant parents must be prepared to make informed decisions about NIPT, including whether to use it and how to address the prenatal care decisions that result from that choice. For some, information from NIPT may inform the decision to undergo additional tests and either prepare for the birth of a child with a serious, potentially life-threatening condition, or end the pregnancy if a condition is confirmed by diagnostic testing. While this has been the case for all forms of prenatal testing, NIPT presents unique challenges to this decision-making process because it provides information about a series of conditions with variable phenotypic severity of which patients have little familiarity (e.g., Turner syndrome, Klinefelter syndrome), as well as providing information about markers of undetermined significance. As with conventional screening, there is the potential for a false positive or false negative result for each of these findings. Furthermore, information gained from NIPT may have unintended consequences by identifying maternal or paternal factors that may be unwanted or unexpected. Previous studies have demonstrated that expectant parents already face a number of challenges in obtaining accurate, unbiased information and decisional support when navigating conventional prenatal genetic screens and diagnostic tests (abbreviated as “prenatal testing” in the rest of this document) and the consequences of being unprepared for a positive test result. This situation has been exacerbated with the introduction of NIPT and will worsen with its expansion. Initially, NIPT was indicated for a subset of the obstetric population, namely women considered high-risk for aneuploidy due to advanced maternal age or reproductive history. Now, NIPT is becoming available for use by the general obstetric population as a primary screen. Clinicians will have to provide individualized counseling to pregnant patients about the advantages and dis-advantages of NIPT compared to other prenatal testing options. As part of this process, they will need to assist patients in placing this information in the context of their goals, values, and beliefs about parenthood, disability, and termination. The magnitude of the resulting challenge becomes evident when considering that over four million women receive prenatal care in the U.S. annually and there are not enough prenatal genetic counselors (GC) or maternal-fetal medicine specialists (MFM) to meet this demand, particularly in rural and urban settings that already face poorer obstetric outcomes due to barriers in access to prenatal care. It is unclear how the medical profession will respond to this unprecedented challenge.

The current situation places a heavy burden on primary obstetric (OB) providers to play a greater role in introducing patients to the option of NIPT and to facilitate decision-making about its use. Already, there are growing numbers of OB providers ordering NIPT, either with or without the involvement of a GC or a MFM, a trend that is expected to continue with the ongoing expansion of NIPT. Thus, an urgent clinical problem has emerged: there is a lack of evidence-based tools to guide OB providers in effective and individualized education and decision support for NIPT. To date, the focus of interventions has been on the development of decision aids and other educational resources to independently educate patients and OB providers about prenatal genetic assessment. These tools may impart information and provide a degree of decision support; however, they do not address the dynamic interaction that leads to the exchange of such information during the clinical visit. Data accrued from our recent work indicate that these strategies do not provide sufficient support or guidance about how to structure effective shared decision-making (SDM) discussions between the patient and OB provider. Studies, including work from our current R21, demonstrate that important barriers exist for patients seeking the information and support needed to navigate their prenatal testing options and make informed, value-reflective decisions about NIPT. While many women are familiar with common autosomal aneuploidies such as T21, they have little knowledge of sex chromosome aneuploidies and

significantly less knowledge of microdeletion syndromes. Patients are overwhelmed by the prospect of learning enough about each of the different conditions that NIPT can detect. As a result, women increasingly rely upon guidance from OB providers with whom they may have an established relationship to help determine which, if any, prenatal testing option to utilize. These are important discussions that take place in the clinical encounter and which educational modules and decision aids alone cannot sufficiently replace. Barriers also exist for OB providers, who report uncertainty about how to provide personalized, effective, and patient-centered counseling about NIPT, particularly under conditions of limited time, reimbursement for counseling, and resources to meet the needs of a diverse population of patients with varying degrees of health literacy and knowledge of genetic conditions, as well as different beliefs about parenthood, disability, and pregnancy termination. Current educational and counseling efforts used by OB providers may not be meeting the self-reported educational needs and decision-making preferences of patients considering NIPT, particularly those pertaining to personal values. Moreover, both patients and providers are concerned about being negatively judged or stereo-typed in discussing topics related to pregnancy termination and infant/child disability, particularly as NIPT increasingly identifies conditions with a range of phenotypes.

The delivery of high-quality, evidence-based prenatal care and access to NIPT will only occur if patients have information and support to make informed, values-based choices about their prenatal testing options. Given that informed decision-making is positively correlated with higher healthcare quality, it is critical to have effective, evidence-based mechanisms that are responsive to the needs and priorities of patients, the day-to-day challenges faced by providers, and the current scientific evidence and clinical practice guidelines about NIPT. While it is recognized that providers should involve patients in healthcare by means of a SDM process, how to achieve that level of communication within the constraints and challenges of the practice of obstetrics remains unknown. Thus, the **goal** of this study is to conduct a cluster, randomized trial to test an evidence-based tool termed NEST (for NIPT Education Support Tool) to support patients' decision-making, focusing on the communication that takes place in the clinical encounter. We will also identify aspects of the patient-provider interaction that are key to implementing effective strategies responsive to the challenges posed by the continued development of NIPT. Our hypothesis is that, by focusing on the dynamic interaction between the patient and provider, NEST will result in a SDM process that, in turn, will both increase patients' ability to make an informed choice about NIPT and decrease the decisional conflict associated with that choice. The expected outcome of this study is a clinically relevant, point-of-care tool that can be utilized among a diverse group of patients and providers to facilitate decisions that are informed, consistent with the patient's values, and with which patients do not experience decisional conflict. This study is significant because the findings and end products will help expectant parents to have informed access to the most recent advance in prenatal genetic science. This project is also relevant to translational research, as informed decision-making is a crucial step in bringing new genetic technologies from the bench to the bedside. We anticipate that this study's findings will ultimately contribute to improving the quality of prenatal care by empowering pregnant women to make informed choices that reflect their needs and preferences as individuals and parents. We also anticipate that OB providers will feel more prepared and confident when approaching conversations about NIPT.

Study Design

<u>Methods</u>

We will conduct a cluster randomized trial to examine the impact of NEST on the decision-making process about NIPT from the perspectives of pregnant women, partners, and providers. As outlined in the initial NIH proposal, our plan is to recruit from multiple healthcare systems. We will begin with Cleveland Clinic. Once we have established streamline recruitment and data collection procedures, we will then extend research activities to the MetroHealth System.

We will utilize the following measures: 1) with the patient's permission, direct observation of the first prenatal visit to measure the primary outcome and 2) a series of surveys to measure secondary outcomes in addition to gain information about the instrument usability and feasibility. The same measures will be used at MetroHealth as they are for the Cleveland Clinic.

PARTICIPANTS AND RECRUITMENT PROCEDURES

Study populations will include the following groups:

I: Pregnant women
II. Partners of pregnant women enrolled in the study
III. OB providers

I. Pregnant women

Study participants will include pregnant women who receive prenatal care at one of the prenatal care outpatient clinics of Cleveland Clinic or MetroHealth. We will utilize the same inclusion and exclusion criteria for the Cleveland Clinic and MetroHealth.

Inclusion and exclusion criteria for this group are as follows:

Inclusion criteria:

1) 18 years of age or older
2) Present for their initial prenatal visit care with one of the providers enrolled in the study
3) Able to provide consent to participate in the study
4) Available for follow-up survey completion in the 1st and 2nd trimester of pregnancy
5) Have a viable intrauterine pregnancy
6) Present for care between 7–12 weeks estimated gestation age (EGA)
7) Ability to read and speak English

Since criteria 5 and 6 will not be determined until the conclusion of the first prenatal visit, women who meet criteria 1–4 will be eligible for participation.

Exclusion criteria:

Women who are:

1) Less than 18 years of age
2) Not currently pregnant or an intrauterine pregnancy has not yet been established
3) Inability to provide informed consent for research participation
4) Inability to speak or read English

Recruitment Procedures:

A. Cleveland Clinic

Per the original protocol, a database will be constructed using the EMR which will include patients' contact information, including MRN, DOB, mailing address, email address and telephone number(s), name of provider and date and place of upcoming prenatal appointment as described in the initial protocol. Initially, recruitment of patients was to take place by mailing a recruitment letter to eligible patients who are scheduled to see one of the providers at the recruitment sites for prenatal care. Given that the study entails identifying women's baseline

knowledge and health literacy with respect to genetics, heritable risk, and the fetal genetic risk assessment process at the first visit, the time to collect these data before the initial prenatal visit is limited. Contact for study recruitment needs to be made in the window before the initial prenatal visit where patients will discuss prenatal testing with their physician or midwife as part of the standard practice of obstetric care. This is a limited window as there is only a short interval of time between when a patient may schedule the initial prenatal visit (e.g., at 7-8 weeks EGA) and the time of her initial prenatal visit (e.g.; 9-10 weeks EGA). Because of this limited window, we therefore need a method of communication that allows for contact with patients who meet the study inclusion criteria in an expeditious manner.

Three options to contact the patients include use of 1) MyChart message, 2) EPIC NEST pool, 3) in person at the clinic visit and 4) Mailers

1) We will recruit participants using MyChart. We will recruit participants by sending an IRB-approved message via MyChart to eligible patients scheduled to see one of the study providers at the recruitment sites for prenatal care. The MyChart message will give a brief overview of the study, the benefits and risks, and give instructions to the patient to contact the Research Coordinator if interested in participation. The interested patient will be sent further information regarding the research study via email or postal mail, based on her preference.

2) We will identify potential participants with the assistance of the call center. We have worked with the patient call center to develop an IRB-approved script for the schedulers to use (Amendment approval # 9). The call center script was developed to aid in recruitment of patients who are scheduling their first prenatal appointment who do not currently use MyChart, our preferred method of contact. This IRB approved telephone script instructs the call center to ask the patient if it would be acceptable for a member of the research team to send them information about participating in a study using the email address or telephone phone number they have on file. If they do not want to be contacted, the scheduler will make a notation in the appointment note that the patient does not want to be contacted. If they want more information, their appointment information gets sent to the NEST pool and the study coordinator will screen the perspective patient.

3) In person recruitment: If we find that responses to the MyChart message are lacking, the Research Coordinator will additionally recruit patients at the time of the first prenatal clinic visit (Amendment #8). She will provide the patient with information about the study (as delineated above), review the informed consent document, and obtain written informed consent from interested patients. We have also incorporated attending child birth education classes at family health centers to boost enrollment if necessary. During the beginning of the class, the NEST study team member hands out the IRB approved NEST study informational brochure.

4) USPS letter: We would like to explore the option of sending a recruitment letter via USPS to the eligible participants. This letter will have the same language as on the MyChart message. This approach will allow us to expand our subject inclusion, including women who may not use MyChart or have an active

MyChart. As studies show an important digital divide among patients who use electronic devices to access healthcare, this will be an important step to broaden representation among our study participants. We will use the USPS letter to recruit the following patients who meet inclusion criteria:

1. Patients who have MyChart, but it is not active
2. Patients who do not have MyChart

In the USPS letter, we plan on using the updated MyChart message included within this amendment, along with our study brochure (previously IRB approved, and has a current stamp).
Once contact is made with the individual, the Research Coordinator will send a written **information sheet** and **brochure** about the study and the **informed consent** for her to review prior to her visit. Based on the individual's preference, these documents can be sent by email, postal mail or overnight courier (e.g. FedEx). The Research Coordinator will meet with patient prior to her 1st prenatal visit to ascertain the patient's understanding of the study procedures and obtain her written informed consent. The informed consent will include information about the opportunity to participate in the direct observation component of the study separate from the survey portion of the study. The direct observation entails audio-recording the discussion between the patient and obstetric care provider regarding prenatal genetic testing.

If no response is received within 72 hours of the MyChart message, a second identical MyChart message will be sent to the patient. If no response is received after the second MyChart message, the Research Coordinator will attempt to meet the patient at the time of her appointment (see section 2, below).

Electronic Email Consenting:
This method of enrollment will only occur if and when a participant cannot arrive early to their first OB appointment, or, if there is a time overlap in recruitment.

Informed consent will be obtained prior to data collection for this phase of the NEST study. Written informed consent will be obtained prior to data collection. The Research Coordinator will email a copy of the consent form to a participant who has already expressed interest in the study by responding to the initial MyChart message.

Once received, the participants will be instructed to review the informed consent, and to ask any questions about the study to the Research Coordinator. If they are still interested in participating in the study, the potential participant will be given written instructions to indicate their choice on whether to opt in or opt out of audio recording by checking the desired box and adding their initials besides it, and to print, sign and date on the lines of the participant of the informed consent. Once this is completed, the participant will return the informed consent to the Research Coordinator. The signed document can be returned to the research team by: 1) mailing it in by USPS in a stamped envelope, 2) scanning or capturing an image the document and emailing it to the Research Coordinator, or 3) faxing it to the Research Coordinator.

Once the Research Coordinator receives a copy of the signed consent, the Research Coordinator will review the consent form to make sure everything is correct. Then, the Research Coordinator will sign and date the consent form under the lines for person obtaining

consent. Finally, the Research Coordinator will send a completed copy back to the patient for their records.

Once the informed consent is completed with both sets of signatures and the decision regarding audio recording, the research coordinator will send the participant their pre-appointment survey(s) (QBASE only for control patients, NEST and QBASE for intervention patients).

Due to the presence of COVID-19 currently in Ohio, but loosened guidelines we will re-instate recruitment procedures at CCF for NEST and control groups using electronic consent and offering audio to patients once again. We will limit our recruitment efforts to electronic outreach and consent only and will have patients fill out the survey electronically, as designated in the original protocol. We will go to the study site in person if the patient has opted for audio-recording or if the patient needs the NEST survey given to them.

B. MetroHealth

We will utilize the same approach used at Cleveland Clinic to recruit pregnant women at the MetroHealth (MH) System with a few exceptions. These procedures have been discussed and agreed upon in conjunction with Dr. Edward Chien who is a co-investigator as listed on the initial NIH application and the former site PI at MetroHealth and will be maintained by the new site PI, Dr. Angela Ranzini. The language of the initial MyChart message will be slightly different, as the MetroHealth team believed this rewording could improve patient recruitment. Another key difference is that MH's system uses a call center but also PRS's, OB nurses, and selected research team members to scheduled patients. These parties will be given the MH specific phone script to inform patients about the study at the time of scheduling. If the patient would like further information on the study after scheduling, the scheduler will pass the patient information through to the MH study coordinator. These procedures have been discussed and agreed upon in conjunction with Dr. Edward Chien, co-investigator as listed on the initial NIH application and the former site PI at MetroHealth and will be maintained by the new site PI, Dr. Angela Ranzini.

Informed consent procedures for pregnant participants: All participants will be asked to provide their written informed consent prior to participation in the study. Informed consent will be obtained using an IRB-approved consent document by a trained research team member and obtained prior to data collection procedures. For pregnant patients and partners, this will take place prior to the scheduled clinical visit.

The original informed consent included authorization for both components of the study: survey completion and audio-recording the discussion during the prenatal visit about prenatal testing. In an effort to include participants who may want to complete the surveys but not have audio-recording, we have modified the informed consent document to designate participation in the survey component of the study with or without audio-recording (Created during the IRB renewal in June/July of 2018).

Electronic Email Consenting:

This method of enrollment will only occur if and when a participant cannot arrive early to their first OB appointment, or, if there is a time overlap in recruitment.

Informed consent will be obtained prior to data collection for this phase of the NEST study. Written informed consent will be obtained prior to data collection. The Research Coordinator will

email a copy of the consent form to a participant who has already expressed interest in the study by responding to the initial MyChart message.

Once received, the participants will be instructed to review the informed consent, and to ask any questions about the study to the Research Coordinator. If they are still interested in participating in the study, the potential participant will be given written instructions to indicate their choice on whether to opt in or opt out of audio recording by checking the desired box and adding their initials besides it, and to print, sign and date on the lines of the participant of the informed consent. Once this is completed, the participant will return the informed consent to the Research Coordinator. The signed document can be returned to the research team by: 1) mailing it in by USPS in a stamped envelope, 2) scanning or capturing an image the document and emailing it to the Research Coordinator, or 3) faxing it to the Research Coordinator.

Once the Research Coordinator receives a copy of the signed consent, the Research Coordinator will review the consent form to make sure everything is correct. Then, the Research Coordinator will sign and date the consent form under the lines for person obtaining consent. Finally, the Research Coordinator will send a completed copy back to the patient for their records.

Once the informed consent is completed with both sets of signatures and the decision regarding audio recording, the research coordinator will send the participant their pre-appointment survey(s) (QBASE only for control patients, NEST and QBASE for intervention patients).

Due to the present of COVID-19 currently in Ohio, but loosened research restrictions, our MetroHealth team will now enroll NEST and Control patients either electronically or in-person (due to limited patient availability with electronic consent). MH patients will also be given the option of audio-recording. The MH research coordinator will present before the appointment if the patient is consented in person or needs the audio-recorder. If the patient enrolls electronically and does not wish to do audio, the MH research coordinator will send all forms electronically. If the patient does complete the forms electronically and does NOT consent to audio, the research coordinator will not present to the appointment to limit personal contact. The research coordinator will scan the completed NEST survey into the patient's chart on EPIC via Onbase. The coordinator will send an in-basket message to the provider saying that the survey was scanned in, and the coordinator will receive confirmation that the provider has received it.

<u>If the first prenatal visit, for whatever reason, becomes a virtual visit,</u> it will be documented and the following changes will be applied:

- Direct observation by means of audio recording will not be conducted. Therefore, the virtual visit will not be recorded in any way for the purpose of this study.
- Once the patient has sent the MH team her signed consent form electronically, they will send her the fully signed consent and links to the REDCap surveys 'NEST' and 'QBASE' with instructions to complete the NEST survey first (if applicable based on group).
- The research coordinator will scan the completed NEST survey into the patient's chart on EPIC via Onbase. It will be located in media manager and be linked to their appointment so the provider can view it before the appointment time. The coordinator will send an in-basket message to the provider saying that the survey was scanned in, and the coordinator will receive confirmation that the provider has received it his or her responding on there.

- The MH research coordinator will also send the completed NEST survey to the patient via email with instructions to use it during the discussion of prenatal genetics during their virtual visit.

II. Partners of pregnant patients enrolled in the study

Study participants will include partners of a patient participant who are (1) directly involved in the patient's prenatal care decision-making and (2) accompany the patient at the first prenatal visit.

Inclusion and exclusion criteria:

Inclusion and exclusion criteria are as follows:

Inclusion criteria:

1) 18 years of age or older
2) The male or female partner (such as partner or mother/aunt/grandmother serving in the role of primary collaborative decision-maker in place of a partner) of a pregnant woman who has participated in the research
3) Participating in decision-making about the pregnancy
4) Ability to read and speak English
5) Ability to provide informed consent for research participation

Exclusion criteria:

1) Younger than 18 years of age
2) Not currently involved in the pregnancy or decision-making about prenatal care
3) Inability to speak or read English
4) Inability to provide informed consent for research participation

Recruitment procedures:

If the patient has a partner (as defined by the patient) and provides permission to contact him/her, the research team member will provide the participant with the study information sheet to give to her partner. As part of the informed consent procedures with patient-participants, the Research Coordinator will inquire about the presence or absence of a partner, his/her involvement in prenatal decision-making, and the pregnant participant's receptivity to the possibility of the partner's involvement in the study as a research participant. If she is agreeable to this, the Research Coordinator will provide the pregnant participant with a recruitment flyer for the partner which will include information about the study which she may share with her partner at her discretion. This flyer will contain instructions for the partner to contact a member of the research team if interested in participation. Pregnant women-participants will be informed that the partner will not be contacted without their permission and that their participation is not contingent on the presence or availability of a partner. If the patient does not mention a partner before the enrollment meeting prior to the first prenatal visit, but brings her partner to the meeting/ appointment, the research team member present will ask the patient if she would like to extend a participation offer to her partner as well. If she gives permission, the research team member will extend a participation offer to the partner.

Informed consent procedures: All partner participants will be asked to provide their written informed consent prior to participation in the study. Informed consent will be obtained using an IRB-approved consent document by a trained research team member and obtained prior to data collection procedures. For partners, this will take place only with the patient participant's consent and prior to the scheduled clinical visit either electronically or in the pre-appointment meeting with the research team member.

Due to the current presence of COVID-19 in Ohio, we will only be offering electronic based consent to patients, partners will continue to be excluded until further notice.

III. OB providers

OB providers who meet the following inclusion criteria will be enrolled:

Inclusion criteria:
(1) OB/GYNs, certified nurse midwives (CNM), and nurse practitioners (NP)
(2) Provide outpatient obstetric care, and
(3) Practice at one of the outpatient clinics of the study sites.

Exclusion criteria:
(1) OB/GYNs, CNMs, and NPs who do not currently provide prenatal care
(2) Medical students, residents, and fellows
(3) Hospitalists who do not provide outpatient obstetric care

We will utilize similar but tailored recruitment approaches for the participating healthcare systems:

Cleveland Clinic:

1) The research coordinator will send a recruitment email describing the nature of the study to each provider who meets inclusion criteria. This initial message also includes the consent form for them to review.

2) In addition, Dr. Ruth Farrell, the Study PI, will be involved in recruitment of OB providers (Amendment #4). Dr. Farrell will present the study at staff meetings of the OB/GYN and Women's Health Institute and encourage her colleagues to participate in the study. While Dr. Farrell is the Vice Chair of Clinical Research for the WHI, none of the OB providers in the subject pool directly report to her. In addition, she is not involved in this populations' professional/performance review or is she in a supervisory role over these individuals. This plan has been discussed with the IRB staff prior to the amendment submission to determine its appropriateness. Dr. Farrell will also send an IRB-approved follow-up email to providers who do not respond within one week to the initial email sent by the research coordinator (Amendment #4).

3) We would like to initiate a new approach to support successful recruitment: utilizing a paper version of the recruitment package, including our recruitment letters (previously IRB approved, and with a current stamp). This recruitment package would be sent to the eligible provider either through 1) Cleveland Clinic interoffice mail, 2) USPS, or, 3) Hand delivery to office manager or assistant

Since our initial recruitment efforts in 2019, the WHI has on-boarded a large number of new OB providers. We would like to reach those providers in addition to existing providers who did not respond to the initial recruitment emails and those who voiced initial interest the study but did not follow up to our recruitment efforts. In this process, we would NOT contact any providers who communicated that they did not want to be in the study or did not want to be contacted by the research team. We will only be reaching out to eligible providers who:

- Eligible providers who have never been contacted by the Research Coordinator regarding participation in this study (new staff since 2019).
- Providers who were previously sent recruitment information, expressed interest but never completed the informed consent process.
- Providers who were previously sent recruitment information but did not respond to that communication.

Once the provider responses to the initial e-mail with a signed copy of their informed consent for study participation, the research coordinator will send a copy with her signature back to for the provider to keep in their records and a copy will be kept on file in a locked cabinet in the NEST office at WHI.

MetroHealth:
The following recruitment procedures have been developed in conjunction with Dr. Edward Chien, co-investigator on the NIH application and former site PI at MetroHealth, and will be maintained by the new site PI, Dr. Angela Ranzini.

1) The research coordinator will send a recruitment email describing the nature of the study to each provider who meets inclusion criteria. The email will also include the consent form for the provider to review.

2) In addition, Dr. Angela Ranzini, the site PI, will be involved in recruitment of OB providers. Dr. Ranzini will send an IRB-approved follow up email to providers who do not respond within one week to the initial email sent by the research assistant.

The research coordinator will obtain the providers' written informed consent for the study participation; a fully signed copy will be provided to the provider and another copy will be kept on file in a locked cabinet in Dr. Ranzini's office at MetroHealth.

Following recruitment and informed consent procedures, OB providers will be randomized by practice into one of two study arms: (1) the intervention arm utilizing NEST or (2) the control arm utilizing standard practice patterns for education and counseling (usual care). Randomization by practice will prevent contamination between study arms, as a patient may see more than one provider within a practice over the course of her pregnancy. A cluster will be an outpatient clinic and contain the providers who practice at that location. The intervention will be delivered to the cluster as a whole. Thus, all participating providers within a cluster will be randomized to the same arm. Practices within the healthcare system will be stratified by both practice and patient-population characteristics. A binary random number generator will be used to assign NEST or control status at the practice level. The assignment will be checked to ensure a balance with respect to the number of clusters and providers in each of the study arms. Imbalances will be corrected manually, and the resultant groupings will be checked to ensure that randomization has been preserved. Participating providers in practices randomized to the intervention arm will receive a training session to orient them to NEST prior to data collection activities. Because NEST is targeted to affect the patient-provider interaction, study participants will not be blinded to which group they have been allocated.

All participating providers at Cleveland Clinic and MetroHealth will be asked to review the most current clinical practice guidelines as developed by the American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medicine (SMFM). These guidelines will be emailed to each provider once their first patient has expressed interest in participating.

We will return to previous methods of enrolling providers into the NEST study at both MH and CCF.

DATA COLLECTION INSTRUMENTS AND PROCEDURES

We will utilize the same data collection instruments at both the Cleveland Clinic and at MetroHealth.

I. Pregnant participants

Data collection instruments and intervention:
We will utilize a series of questionnaires to assess the study outcomes. This includes the questionnaires administered at different stages of pregnancy in addition to the intervention. These were developed by the following procedures:

Dr. Farrell and her research team, with the input of the study Co-Investigators and members of the Advisory Panel, developed draft instruments based on existing validated instruments in the literature. Specific instruments include:
(1) Multidimensional Measure of Informed Choice (MMIC), a validated tool that uses to multiple choice and Likert-scale items to measure knowledge, attitudes, and decision-making associated with prenatal genetic testing
(2) Decisional Regret Scale (DSC), a validated scale using Likert-scale items to measure satisfaction/regret with the decision-making process (not the outcome of the decision).
(3) Medical Term Recognition Test (METER), a validated tool used to assess health literacy. In METER, a list of 70 terms are given to a participant that contain some real medical words (i.e. words that have to do with body parts, body functions, types of diseases, etc.). The list also contains some items that may look or even sound like medical words but are not actually real words. The participant is given instructions to place an "X" next to the words they recognize to be real words. The participant is also told they should not guess and to only put an "X" next to a word if they are sure it is a real medical word.

Questionnaire development involved a process of modifying the MMIC. Because the MMIC developed several years ago, modifications were required to ensure that the instruments were able to assess primary and secondary outcomes. Initial survey items were developed through a consensus-building process among the study co-investigators. The instruments were then tested through a process of cognitive interviews (Amendment #1). The draft instrument was revised based on this process and then utilized for data collection. The finalized instruments were approved for use by the IRB (Amendment #5).

The data collection instruments are as follows:

a. Baseline questionnaire **(Q_{BASE})**: This survey will collect the following information: (1) participant demographic and reproductive history information, (2) healthcare decision-making preferences, (3) participant knowledge and (4) familiarity with the concept of shared decision-making.

b. Post initial visit questionnaire (**QPV**): This survey will collect the following information: (1) participant knowledge, attitudes, and decision-making regarding NIPT (alternative tests or no testing), (2) health literacy.

c. Time of testing questionnaire (**QTT**): This survey will collect the following information: (1) participant knowledge, attitudes, and decision-making regarding NIPT (alternative tests or no testing) and (2) decisional regret.

d. Follow-up questionnaire (**QFF**) This survey will collect the following information: (1) participant knowledge, attitudes, and decision-making regarding NIPT (alternative tests or no testing) and (2) decision-making regret.

Measures	**Baseline (QBase)**	**Post visit (QPV)**	**Time of test (QTT)**	**Follow up (QFF)**
Demographics	X			
Shared decision-making and decision-making preferences	X	X	X	X
Informed choice/MMIC		X	X	X
Decisional regret/DSC			X	X

Study Intervention: We will also utilize the following questionnaire as the study intervention. The intervention (NEST) is also a questionnaire. NEST is a point of care shared decision-making tool. NEST is structured as a self-administered survey completed by the participant prior to the initial prenatal visit. Survey questions pertain to baseline knowledge of concepts associated with NIPT, fetal genetic risk and assessment, and decision-making preferences and priorities with respect to prenatal testing. NEST is divided into three sections. Section 1 contains a series of questions to ascertain patients' familiarity with: the different prenatal genetic screening and diagnostic tests; the conditions that can be detected using prenatal screening and testing, as well as terms uses to describe these tests. Section 2 addresses informational and decision-making priorities to set the agenda of the conversation. This section addresses concepts associated with scientific and medical aspects that form the basis of decisions about NIPT and alternate prenatal tests. Section 3 contains open-ended questions so that the patient can provide additional information, as well as questions to further personalize the discussion. Those participants who are seeing a doctor or midwife randomized to the intervention arm may complete NEST online at the time of completing QBASE or on a secure iPad in the clinical area before the initial prenatal visit. A printed summary of the NEST data reporting the patient's needs and priorities will guide the provider to structure a patient-centered shared decision making process. The NEST report will be generated from the data entered into the NEST using REDCap survey. It will contain no other information but merely be a presentation of the pregnant patient-entered data. The research assistant will print the NEST Report and review it with the pregnant patient. The patient will be provided with a copy of the NEST Report to reference during the visit and to share with her partner based on her preferences. As part of the informed consent procedures, the pregnant woman will be made aware that she does not need to share this information with her partner as part of study procedures. A copy of the NEST Report will then be given to the provider to review prior to the clinical visit to tailor the content and focus of the discussion with the patient about her different screening and testing options.

Data collection procedures:

1) QBASE: Once informed consent has been obtained, all participants will complete the QBASE. This will be administered on a CCF-compliant tablet and using REDCap survey. The research team member does come with a paper copy of the QBASE as a backup for any technical difficulties. If the paper survey is used, it would be manual entered by the research team into REDCap.

2) NEST Intervention: Participants scheduled to see an OB provider randomized to the NEST (randomization occurs at the level of the OB provider) will be asked to complete the NEST. This will be administered on a CCF-compliant tablet and using REDCap survey. After completion, patient participant will be given two printed copies of the NEST, one for the patient and one for their provider, to review during their office visit. The participating provider will be given a copy of the NEST to help tailor the conversation to the patient's needs. Patients who are scheduled to see a provider at a practice randomized to the control arm will receive standard care.

As recent guidelines have changes, we will again be enrolling patients from designated intervention branches for the CCF and MetroHealth sites.

As a follow-up measurement, the Cleveland Clinic study team will conduct semi-structured interviews (Amendment #14). In doing so, we will gain further understanding of the decision-making process for prenatal genetic tests in addition to gain further information regarding the usability, feasibility and acceptability of the NEST intervention. Participants will include women who meet the criteria for the NEST study, and are either: in the 3rd trimester of pregnancy or have delivered in the last 12-months. This population reflects women who have completed the prenatal genetic test decision-making process and can provide key insight into ways to improve the best support that process. We will contact participants who meet inclusion criteria regarding participation in in-depth telephone interviews via MyChart or email, whichever has been the approved method (by the participant) for contact as part of the NEST study. Before re-contacting is initiated, a research team member will review to determine if individuals meet inclusion criteria. This will include a review of 1) the medical record of eligible participants to determine if any obstetrical complication has occurred that would constitute exclusion and 2) the research documentation to determine if an eligible participant withdrew or was withdrawn from the NEST study. These individuals will not be re-contacted.

3) Direct observation: We will use a method of direct observation (DO) to measure shared decision-making, the primary outcome of the study. We will measure this by audio-recording the visit and then using (1) the OPTION scale, a validated scale of shared decision-making and (2) a content checklist to assess the content and discussion of the visit. See Data analysis below for further description.

We will audio record patient-provider discussions during the first prenatal visit of those patients who provide written informed consent to do so. The research assistant will give the recorder to the patient to record the content, interaction, and duration of dialogue pertaining to genetic risk and risk assessment. We have elected to audio record instead of video record in an attempt to minimize the Hawthorne effect and because of the sensitive nature of the physical exam that takes place during this visit. Patients are given the option

to either (1) record the whole appointment. If this happens the research assistant will only transcribe the dialogue pertaining to prenatal genetic screening, or, (2) to turn on the recorder when the discussion regarding prenatal genetic screening is taking place.

As recent guidelines have changes, we will again be offering patients the option to consent to audio-recording during their first visit for the CCF and MetroHealth sites.

4) QPV: This survey will be administered approximately 7-10 days following the first visit when the basic concepts associated with prenatal genetic testing have been introduced. It will be administered using online REDCap survey. Unless otherwise specified by the participant.

5) QTT: This survey will be administered between weeks 12-22 EGA once the participant has made a decision about if to undergo prenatal genetic testing (or at the EGA at which the opportunity has closed in the case of those participants who elect against testing). It will be administered using online using REDCap survey. Unless otherwise specified by the participant.

6) QFF: This survey will be administered between weeks 22-24 EGA. It will be administered using online using REDCap survey. Unless otherwise specified by the participant.

A review of the medical record will be conducted prior to communication about each survey to ensure that the participant continues to meet inclusion criteria. Individuals who experienced a complication or fetal demise as documented at the time point of QPV, QTT and QFF, or who no longer receive care at the Cleveland Clinic or MetroHealth, depending on original site of enrollment and will not be contacted to complete the survey(s). Each study site, either Cleveland Clinic or MetroHealth, will be responsible for all subsequent chart reviews and administration of all QPV, QTT and QFF surveys for all participants enrolled at those sites. All patients will receive a research stipend of the following amounts for each of the completed surveys from the Cleveland Clinic Accounts Payable Offices (patients will receive <u>up to</u> $150.00):

1) QBASE - $25.00
2) QPV - $25.00
3) QTT - $50.00
4) QFF - $50.00

II. Partners of participating pregnant patients

We will utilize the same data collection instruments and procedures at both the Cleveland Clinic and MetroHealth.

<u>Data collection instruments</u>: This includes the QBASE and QPV, both identical to the questionnaires administered to pregnant participants.

<u>Data collection procedures</u>:

1) QBASE: Once informed consent has been obtained, participants will complete the QBASE. This will be administered on a CCF-compliant tablet and using REDCap survey. Partners will complete their own survey independent from the pregnant participant.

2) Direct observation: Partners will be included in the DO as they will be present for the visit (see above for details).

3) QPV: This survey will be administered approximately 7-10 days following the first visit when the basic concepts associated with prenatal genetic testing have been introduced. It will be administered using online using REDCap survey. Unless otherwise specified by the participant.

All partners will receive a research stipend of the following amounts for each of the completed surveys from the Cleveland Clinic Accounts Payable Offices (partners will receive up to $50.00):

1) QBASE - $25.00
2) QPV - $25.00

Of note, partner-participants will complete each of these instruments separate from the pregnant-participant. Responses will not be shared among a patient-partner pair.

Due to the presence of COVID-19 in Ohio, we will temporarily suspend recruitment of partners.

III. OB providers

We will utilize the same data collection instruments and procedures at both the Cleveland Clinic and MetroHealth.

Data collection instrument:

OB providers will complete a baseline questionnaire, OBP, at the time of enrollment. This survey will collect the following information: (1) prenatal appointment discussion points, (2) provider familiarity, (3) provider confidence in prenatal testing topics, (4) opinions on advancing prenatal genetic tests, (5) shared decision-making, and (6) decision-making preferences.

Data collection procedures:

Once the OB provider sends back their signed informed consent agreeing to participate in the study, the research coordinator will send the OB provider a link through REDCap. This link will take the OB provider directly to the OBP questionnaire and can complete the survey electronically on any internet connected device, unless otherwise specified (we are able to give the providers hard copy of the survey, and those providers can either scan and email the completed survey to their respective research coordinator or via a fax number provided to them by the research coordinator). Once completed, the study coordinator will have their responses to the survey on the NEST study restricted drive and will move forward with gift card purchase. After the survey is completed and saved, the research coordinator will send a $50.00 amazon gift card in appreciation to the OB provider for their participation in the study and the completion of their OBP questionnaire. For the MetroHealth providers, the MetroHealth research coordinator will send a weekly report to the Cleveland Clinic research coordinator containing a list of names and emails of the providers that need to be sent their amazon gift card.

For providers assigned to use the NEST communication tool, they will be sent a short feasibility survey (OBP-F) to assess if they are using the NEST. This survey will be sent once the provider has had a respectable amount of time participating in the study.

Due to the presence of COVID-19 in Ohio, we will conduct consenting and survey procedures through electronic options previously approved for CCF. Our MetroHealth sites will be allowed to recruit electronically or in-person based off of the MH research re-installment policy. All follow-up surveys (QPV, QTT, QFF, OBP, OBP-F) will be sent to participants electronically. They will still receive stipends, but we know that their will likely be a delay in the usual turnaround time for the stipends, so when participants complete a survey they will be informed by their site study coordinator (either CCF or MetroHealth) that their survey was received but due to the COVID-19 outbreaks there will likely be a delay for them to receive the stipends.

DATA ANALYSIS

Data Analysis

Data from the surveys will be collected either 1) using a tablet PC enabled with REDCap Survey for direct data entry or, if necessary, due to technical issues 2) on paper surveys with manual entry by the research team into REDCap. This is only done if there is a technical issue with the iPads or printers (internet connectivity problems, battery issues, etc.).

The following analysis will be conducted with the Principal Investigator in conjunction with Meng Yao, the QHS statistician designated to the WHI using JMP and SAS:

Data from the direct observation will be analyzed using the *observed* OPTIONS scale. This is a validated scale similar to the *dyadic* OPTIONS scale but developed for direct observation measurement of SDM in the clinical encounter. The *observed* OPTIONS scale will be utilized in conjunction with a content checklist to determine if the information exchanged during discussions of prenatal genetic risk and assessment meets the needs and preferences of patients, the recommendations of OB providers and GCs published by the American College of Obstetricians and Gynecologists, and clinical practice guidelines. The checklist was developed using data from our preliminary studies.

Audio recordings from the direct observation will be transcribed verbatim for analysis. Transcriptions will be coded by two independent coders using the *observed* OPTIONS scale and content checklist. Measures will be analyzed as a function of exposure (NEST vs. control) and visit composition (patient only vs. patient/partner pairs). The content checklist will be utilized to assess discussion content and to determine fidelity to the intervention. Transcriptions will be time-stamped to determine the length of discussions pertaining to prenatal genetic risk and assessment in NEST vs. control groups. Tukey-Kramer comparisons will be made to adjust for multiple comparisons. The matrix of predictor variables of intervention, patient characteristics, including variables of baseline knowledge and attitudes, presence of partner at the visit, and provider characteristics will be examined using the co-linearity tests of variance inflation factors and condition indices. Those variables exhibiting sufficient independence will be included in the multivariable analysis. Kappa statistics will be calculated to assess the degree of agreement between the coders; a third coder will be brought in if consensus cannot be reached.

For those patients/partners and providers who both opt-in to direct observations, the audio will be summed in accordance with the OPTIONS scale instructions, and the results for patients/partners and providers will first be analyzed separately as a function of intervention (NEST vs. control).The data from patients/partners and providers will be combined in a data set matching patient and provider responses. The difference between matched pairs will be computed for SDM broadly, and components of SDM as described by OPTIONS will be computed individually, sorted by type of intervention, and, with the t-test, checked to see whether, within study arms, the means of the differences are significantly different from zero.

DATA MANAGEMENT

All study information will be maintained in a secure fashion as delineated by the Cleveland Clinic IRB, either in a locked cabinet in the WHI or on a secure, encrypted research computer. We will use IRB-approved level of encryption on the computer. Only research personnel will have access to these files. In addition, all personal identifying information recorded per IRB and informed consent purposes will be kept in a separate location from data to be used for analysis purposes.

Confidentiality of patient information will be maintained at all times. The study will have Institutional Review Board approval prior to recruitment of any patients at participating clinical sites. All study investigators and research team members will document completion of Human Subjects Protection Training prior to initiating any study procedures. This requirement may be met by completing the NIH course, the CITI (Collaborative Institutional Training Initiative) program, or another course as required by the member institution.

Cleveland Clinic:

Masterlist: A master list will be maintained that will allow researchers to link participants with their ID numbers only for the following purposes:

1) Documentation and distribution of gift card/ research stipend in appreciation of subject's time and participation in the study.

2) To link pregnant participants' and clinicians' responses during the data analysis phase as needed. Any linkage will be de-identified after data analysis is complete.

3) To investigate any adverse events: A data safety and monitoring protocol has been put into place. If any adverse events are identified, then the master list will be used to link the participant with her personal identifying information for this purpose.

The master list will be stored on the WHI shared drive with encrypted, IRB-approved research computers in the WHI at the Cleveland Clinic as described above. All paper documents (e.g., informed consent documents) will be kept in a locked storage cabinet in the WHI and only research personnel will have access to them.

Informed consent documents: These documents are stored electronically on the designated Research team folder within the secured and encrypted shared drive of Cleveland Clinic WHI. Physical copies of all consent follow IRB procedures of storage; locked in the NEST research office of the WHI and only accessible by research personnel.

NEST data: NEST is completed on a secure Cleveland Clinic registered tablet through the secured REDCap survey program. All data collected as part of the NEST on the tablet device will be downloaded to the secure Cleveland Clinic server and deleted from the device immediately. One printed copy goes to the patient for her records, the other copy is given to the provider with instructions to shred after discussion with patient.

Questionnaire data: All other questionnaires (QBASE, QPV, QTT, QFF, and OB provider survey) are completed on a secure Cleveland Clinic registered tablet or through the secured REDCap survey program. These documents are saved electronically on the secured shared drive of the WHI in the research team's folder and on the secured REDCap server. All research team members have gone through IRB approved training to handle data management and secure patient information.

Audio-recordings: Audio-recordings will be downloaded to the secure Cleveland Clinic server and deleted from the device immediately. Additionally, any personal identifying information will be permanently deleted from the audio-recording and will not be available for transcription. No data will be stored on the recording devices. All data for analysis will be de-identified. Participants will be assigned a unique ID number at the time of enrollment. Inadvertent disclosure of personal identifying information during the initial prenatal visit will be edited from the transcript and will not be retained.

MetroHealth:

Initial recruitment and data collection procedures will be conducted at MetroHealth and by the MetroHealth research team. This will include identifying and contacting eligible participants, initial recruitment activities, obtaining informed consent, and administration of QBASE and NEST when applicable. All subsequent chart reviews and continuing communication with the distribution of all follow up surveys (QPV, QTT and QFF), will be conducted by the MetroHealth research coordinator. The direct observation transcriptions and all research stipends for patients and partners, and gift card for OBP completion for provider participants will be completed by the Cleveland Clinic research coordinator. A detailed work flow and procedure chart between Cleveland Clinic and MetroHealth will be included at the end of this protocol.

Masterlist: There shall be a Masterlist identical in format to the Cleveland Clinic research team's original Masterlist. The MetroHealth Masterlist shall solely be for MetroHealth participants (patients, partners, and providers). The MetroHealth Masterlist will be stored in the same manner the Cleveland Clinic Masterlist is stored; on a secure, restricted data storage folder, which only those involved in the study at their specific sites (MetroHealth or Cleveland Clinic) will have access to. When MetroHealth enrolls a patient they will begin a new record in the REDCap instrument "METROHEALTH Study Visits" under the project titled "NEST Participant Active Worksheet". The MetroHealth research team will only have access to this instrument in the 'NEST Participant Active Worksheet' project. This project mirrors the Cleveland Clinic's Participant Active Worksheet completed manually in excel and used to monitor all study participant completion status. Once a week, a Cleveland Clinic research team member will physically go to the MetroHealth designated office for this study to collect an enrollment report and other documents. During the weekly visit, the research coordinator at MetroHealth will give a report to the Cleveland Clinic research team member. This report will include the names of

providers and participants which require research stipends and which stipend they require (i.e. John Doe for completion of QPV).

Informed consent documents: During the weekly visit, a Cleveland Clinic research team member will also collect electronic copies of the signed consent forms. The Cleveland Clinic research team member will transfer the signed consents via an encrypted flash drive, and immediately deleted off of the flash drive following saving them on the Cleveland Clinic restricted drive, this is the same restricted drive we have for all Cleveland Clinic participant consents. Cleveland Clinic will maintain study documentation for all participants (patients, partners, and providers) enrolled in the study and will keep documentation stored on a secure drive for data storage. Any paper copies will be in a locked cabinet in the NEST office of each designated site. This is required to have to complete accurate quality assurance checks.

NEST data: Data associated with NEST will be completed by the consented participant on a Cleveland Clinic /IRB approved iPad or on the participants personal internet connected device for surveys sent after their first OB appointment and the data will be stored via the Cleveland Clinic REDCap database. The MetroHealth research team's access to the REDCap database will be limited to only manually input data as needed, and, to be able to view and download only the data from the NEST questionnaire. All other functions will be disabled so that access to the data will be restricted to the Cleveland Clinic research team.

Questionnaire data: All surveys (OBP, NEST, QBASE, QPV, QTT and QFF) distributed by MetroHealth will be completed by the consented participant on (1) a Cleveland Clinic /IRB approved iPad and will be stored via the Cleveland Clinic REDCap database, (2) on a paper copy, only in the event of technical difficulties, or (3) via an emailed web-link that will take the participant directly to the survey through REDCap. The MetroHealth research team's access to the REDCap database will be limited to only manually input data as needed, and, to be able to view and download only the data from the NEST questionnaire.

Audio-recordings: MetroHealth will used the same Cleveland Clinic/IRB approved audio recording devices and will store the audio on their secure drive for data storage in the same manner as Cleveland Clinic. The clinical visit will be digitally audio-recorded as part of the direct observation component of the study and directly downloaded from the recorder to a MetroHealth password-encrypted study computer using a direct USB port. During the weekly visit, the Cleveland Clinic research team member will transfer the direct observation audio files on MetroHealth secure drive via an encrypted jump drive provided by Cleveland Clinic to a Cleveland Clinic laptop, saved on a secure drive for data storage.

All study information will be maintained in a secure fashion as delineated by the Cleveland Clinic IRB: either in a locked cabinet in the OB/GYN and Women's Health Institute or on a secure, WHI shared drive accessible only by IRB approved research team members. All data collected as part of the NEST on the tablet will be entered and saved into the secure Cleveland Clinic REDCap. No data will be stored on the tablet. In a similar fashion, all data will be immediately downloaded and removed from the audio-recording device used as part of the direct observation component of the study. This procedure has already been confirmed and approved by the Cleveland Clinic Research Compliance Office.

Only members of the research team at Cleveland Clinic or at MetroHealth will have the ability to access this information. Access to research data will be restricted to members of the research team who are knowledgeable about applicable federal regulations and institution policies governing the involvement of human subjects in research.

No information will be shared in the course of this study with anyone outside of the study staff. We have also taken into consideration the participation of partners in this study. The pregnant woman and her partner will be aware of the decision to participate in the study and that the content of the discussion that takes place during the clinical encounter that will be audio-recorded as part of the direct observation component of the study. No data from the pregnant woman participant will be shared by the research team with her partner and vice versa.

All data will be de-identified and reported in aggregate. No participants will be identified by name in any research reports or publications about the study.

OVERSIGHT RESPONSIBILITIES

Oversight of the study will be provided by the Principal Investigator, Dr. Ruth Farrell, and the study co-investigators.

MONITORING PROCEDURES

Dr. Farrell will ensure that informed consent has been obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the Principal Investigator and co-investigators to review. The Principal Investigator and co-investigators will review the different aspects of the study conduct on a monthly basis. This will include assessment of recruitment, accrual, drop-outs, and any protocol deviations. The Principal Investigator and co-investigators will review the study procedures and data for any Adverse Events (AEs) as defined below, individually in real-time and in aggregate on a monthly basis. The Principal Investigator and co-investigators will review the study procedures and data for any serious adverse events (SAEs) as defined below in real-time. The Principal Investigator will report all protocol deviations, AEs, and SAEs to the NIH and Cleveland Clinic IRB according to the applicable regulatory requirements.

COLLECTION AND REPORTING OF SAEs AND AEs

Definition of an Adverse Event (AE): As this is a clinical trial of a communication tool, the study and safety issues and adverse events observed are expected to be minimal. That said, we have outlined the following Adverse Events for this study based on standard definitions of AEs as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

An AE for this study includes the following:

- Loss of confidentially of study data between the patient-subject and partner-subject: As described above, the patient-subject and partner-subject will be aware of the decision to participate and aware of the content of discussions that take place as part of direct observation. Both will be informed that there will be no intentional disclosure of information provided on individually completed surveys between the patient-subject and partner-subject.

- Psychological distress necessitating provider-initiated referral or self-referral to Behavioral Health for counseling at any time point in the study: The process of exploring the nature and implications of prenatal genetic testing may cause distress in any patient presenting for prenatal care. We acknowledge that some participants may experience distress from exploring these decisions differently as part of the intervention versus the control, whether that results in a greater or lesser depth of pre-test and post-test consideration and its relation to decisional regret. We also acknowledge that discussions about the goals and implications of prenatal genetic testing may lead to disagreement and distress between a pregnant patient and her partner. Distress that results in referral to Behavioral Health will be considered an AE. This includes referral within the healthcare system as identified by chart review or verbal report of the subject or subjected-initiated referral outside of the healthcare system.

Serious Adverse Event (SAE)

SAEs have been defined in consideration of aspects associated with recruiting a pregnant woman-partner dyad. Given those considerations, any AE that results in any of the following outcomes will be designated as a SAE:

- Suicidal or homicidal ideation with or without action
- Incidence of domestic violence
- Event requiring inpatient hospitalization or prolongation of existing hospitalization

SAEs and specific procedure-associated AEs will be reported to the Data Safety Monitoring Board (DSMB) within 24 hours. In addition, all AEs will be reported according to the Cleveland Clinic IRB AE reporting guidelines.

Classification of AE Severity

AEs will be labeled according to severity, which is based on their impact on the subject according to the following definitions:

Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment, it becomes an SAE.

AE Attribution Scale

AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled not related, possibly related, or related to the study intervention as follows:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

AEs are identified by review of study procedures and the medical record. Review of the medical record will be performed as outlined by the IRB for the purpose of this study to identify any ICD-10 codes or referrals consistent with AEs defined above. AEs will also be identified by verbal report of a subject or subject-initiated referral outside of the healthcare system.

Management of Risks to Subjects

If an AE or SAE is identified, then a process of review of study procedures will take place. This will include review of documentation and storage of materials related to the study. This will also include a review of recruitment and communication practices among the research team to identify if and where possible AEs or SAEs occurred. This will also include review of surveys and transcripts from direct observation to determine the timing and source of the AE or SAE.

AE and SAE Reporting

SAEs and specific study-associated AEs will be reported to the NIH and the Cleveland Clinic IRB within 24 hours. In addition, all AEs will be reported according to the Cleveland Clinic IRB AE reporting guidelines. In addition, all SAEs and specific study-associated AEs will be reported to the Data Safety Monitoring Board.

Data Safety Monitoring Board

A formal, independent Data Safety Monitoring Board (DSMB) has been established with specific expertise in nature of this study and study population to provide oversight for AEs and SAEs. The DSMB will include members with specific disciplinary expertise in:

1) Obstetrics and maternal fetal medicine
2) Research and clinical ethics
3) Clinical genetics
4) Clinical trials
5) Medical decision-making

All SAEs and specific study-associated AEs will be reported to the DSMB for independent review. In addition, the DSMB will have access to study data to conduct review as per their judgment. The DSMB will meet for an in-person meeting every 6 months and provide a report to the investigators following each meeting. This report will summarize any denied AEs or SAEs, issues related to data confidentiality, and issues related to quality issues overall and by site. These summaries will be reviewed by the Principal investigator and co-investigators on a routine basis.

NEST sub-study, follow up interviews with patients who completed the NEST study:

We are submitting this amendment to begin conducting semi-structured interviews to gain further understanding of the decision-making process for prenatal genetic tests in addition to gain further information regarding the usability, feasibility, and acceptability of the NEST intervention. Over the course of our study, we have learned that patients may benefit from educational and decision-making resources at different stages of the prenatal genetic testing decision-making process. As a result of these findings, we would like to gather additional information about the best approach to making educational resources and decision-making support tools available to pregnancy after the initial prenatal visit.

This data is not required to be shared with the NIH.

Methods:

We will conduct a qualitative study using in-depth interviews to gain further understanding of the decision-making process for prenatal genetic tests and further information regarding the usability, feasibility, and acceptability of the NEST intervention. Specifically, we will conduct interviews to explore patient preference regarding the mode and timing of educational resources and decision-support tools used in place of or in conjunction with the NEST instrument over the course of pregnancy.

Study population:

Participants will include women who meet the criteria for the NEST study and are in the 3rd trimester of pregnancy or recently delivered (within the past 12 months). This population reflects women who have completed the prenatal genetic testing decision-making process and can

provide key insight into ways to improve and best support that process. We will not re-contact participants who may have taken part in an interview at an earlier time in the study.

Inclusion and exclusion criteria include:

Inclusion Criteria:

1. 18 years to 45 years old
2. Women who enrolled and completed all parts of the NEST study (IRB #17-987)
3. In the 3rd trimester of pregnancy or delivered within the past 12 months
4. Able to read and speak English
5. Able to provide consent for research participation

Exclusion Criteria:

1. Women younger than 18 years of age
2. Women who were withdrawn from the NEST study as a result of an obstetrical (e.g., miscarriage or pregnancy loss, IUDF, premature delivery) complication
3. Women who withdrew themselves from the NEST study
4. NEST participants who already were recontacted about an interview at an earlier stage in the study
5. Unable to read or speak English
6. Unable to provide informed consent for research participation

Sample size: We will have a target sample size of 40 participants for the in-depth interviews. Based on our prior studies, we anticipate this will be the number at which saturation will be achieved with respect to identification of lead decision-making factors. Interim analysis will be used to determine if additional interviews need to be conducted. Final sample size will be determined by the point at which theoretical saturation has been met.

Recruitment:
We will contact participants who meet the above inclusion criteria regarding participation in in-depth telephone interviews via MyChart or email, whichever has been the approved method (by the participant) for contact as part of the NEST study.

Before re-contacting is initiated, a research team member will review to determine if individuals meet inclusion criteria. This will include a review of 1) the medical record of eligible participants to determine if any obstetrical complication has occurred that would constitute exclusion and 2) the research documentation to determine if an eligible participant withdrew or was withdrawn from the NEST study. Additionally, we will not re-contact participants who may have taken part in an interview done at an earlier time in the study. These individuals will not be re-contacted.

The research team member will send those women who meet inclusion criteria a recruitment letter that describes the study and directions to contact the Research Coordinator (by email, telephone, or MyChart response) if interested in study participation. This letter will be sent via MyChart or email, whichever has been the approved method (by the participant) for contact as part of the NEST study.

The Research Coordinator will document the date of first re-contact. The eligible participant will be sent a follow up message within one week via the preferred contact method documented as part of the NEST study if no response regarding participation has been received. A second follow up message will be sent via the preferred contact method if no response has been received within 7 days of the prior contact. No additional attempts to reach the eligible participant will take place after this point.

Informed consent procedures:
Informed consent will be obtained prior to data collection for this phase of the NEST study. Written informed consent will be obtained prior to data collection. In developing this informed consent process, we are cognizant of the importance to not have patients present for research outside of their scheduled visits and to reduce potential exposure. The informed consent will be obtained via DocuSign (Part 11 Compliant).

The process of obtaining consent will be as follows: Once the eligible participant contact the Research Coordinator, and expresses their interest, the coordinator will send the participant a copy of the informed consent (this will be sent via email or USPS, based on the participant's preferences). After an initial review by the patient, a telephone call will take place between the patient and the Research Coordinator to formally review the consent form and detail the patient's responsibilities as the research participant. Following that phone call, if the patient still wants to participate, the research coordinator will then provide instructions on how the patient will sign the consent via the DocuSign platform (instructions on how to use DocuSign will be sent to the participant). After the document has been signed by all parties, the patient will receive an email notification that the document is complete. The notification will include the completed tamper-sealed PDF as an attachment. Once the consent is signed by both the participant, the Research Coordinator will make sure, (1) a copy of the consent will be sent back to the participant for her records, (2) the signed consent (physical copy) will be kept in a locked file in the Women's Health Institute, and (3) an electronic copy will be saved on the secured WHI shared drive.

Once the informed consent is completed, the patients name and contact will be sent to Dr. Ruth Farrell, study PI, who will work with the patient to schedule time for the telephone interview. Prior to the interview, Dr. Farrell will confirm that the participant understands the nature of the study and is willing to participate in the study and will also confirm the participants identify by verifying their date of birth.

Data Collection:
Dr. Farrell or a member of the research team will conduct a semi-structured interview with the participant. The interview will be structured using an interview guide. Questions will pertain to patient preference regarding the mode and timing of educational resources and decision-support tools used in place of or in conjunction with the NEST tool over the course of pregnant.

As part of the interview, we will ask participant their opinions on how best to support patients across the longitudinal experience of prenatal genetic testing, beginning in the first trimester with the initial decision to undergo testing and ending in the second trimester. To do so, we will ask

participants to review a diagram that provides an overview of the testing process during the interview and provide their feedback on the testing process and concurrent educational/decision support process (see Picture 1). We will instruct the participant to review the picture during the final set of questions. The interviewer will walk the participant through the different testing options, explaining some of the terms and abbreviations on the diagram, and emphasizing both the optional and preference-based nature of the process.

This diagram was developed in conjunction with Marissa Coleridge, prenatal genetic counselor and study co-I, to reflect the testing algorithm in place at the Cleveland Clinic. We will ask participants to have this diagram (see below for how they will receive it) at the start of the interview, both when we are scheduling the interview and at the start of the interview process.

This diagram will be sent to the participant by one of these methods:

1) My email at their preferred email address: We will inform participants that they will receive an email with the subject line “Information for the study interview.” The email will contain a brief message about the attachment and the instructions not to open the attachment until instructed so during the interview.
2) US postal mail: If the participant prefers the diagram to be send via US postal mail, we will mail a paper copy of the diagram in a sealed envelope with the accompanying letter with instructions.

We have also developed a plan if the participant does not have access to the paper or electronic diagram at the time of the interview. In this case, we will ask the participant if we may text a photo of the diagram to her phone. If the participant declines this option and does not want to reschedule the interview, we will not include the question pertaining to the diagram in the interview.

The interview will be audio-recorded for data analysis purposes. The research team member will take field notes during the interview for data analysis. Digital audio files will be immediately downloaded from the Research Compliance approved digital recording device to a secure folder on the WHI shared drive and then deleted from the audio device. This is the same procedure which was Research Compliance and IRB approved for the IRB study #19-139. Audio-recordings will be quality checked. Before the interview begins, participants will be asked not to include any personal identifying information during the interviews by using the IRB approved phone script. Any identifying information inadvertently disclosed by the participant during the interviews will be deleted from the original data file.

Interviews will last 30-45 minutes. Participation will end at the conclusion of the telephone interview. Participants will receive a $50 gift card in appreciation of their time and effort with the study.

Data analysis:

Audio-recordings will be transcribed verbatim and verified for accuracy. The team will approach data analysis as an iterative and progressive process of data immersion, coding, memoing and theme identification, an inductive process consistent with grounded theory. We will identify

content domains and categories in transcripts to create a coding tree that will be used to organize the data. A companion codebook will be created to serve as a reference for analysis. Transcripts and coding tree will be uploaded to NVivo (version 12), a qualitative data management and analysis software package. The research team will hold weekly meetings to review data coding and memoing and identify themes. Themes identified will be contextualized with information about trimester of pregnancy, gravity/parity, and previous pregnancies. Demographic data will be utilized to provide clarification of how findings are predicted by these variables.

Data Access and Confidentiality:
Access to potentially identifiable research data will be restricted to members of the research team who are knowledgeable about applicable federal regulations and institution policies governing the involvement of human subjects in research. No participants will be identified by name in any research reports or publications about the study. Any personal identifying information inadvertently disclosed by the participant during the interview will be permanently deleted from the audio-file. In the informed consent document, all participants will be advised that their decision to participate is voluntary and responses will not be disclosed to anyone outside the research team.

Signed participant consent forms will be kept electronically on the secured WHI shared drive and physical copies will be stored in a locked file cabinet in the office of the Principal Investigator. Any field notes will be entered into the secured Cleveland Clinic REDCap and physical notes will be kept in a locked cabinet in the office of the NEST study team.

Only IRB approved research staff for this study will have access to this information. These data management practices will be used throughout the duration of data collection and data analysis. No participants will be identified by name in any research reports or publications about the study. All data will be destroyed when allowed by institutional regulations.

Data management:

Data from the interviews will be collected with field notes and entered using NVivo and Word. A master list used to track of inclusion criteria, informed consent, data collection, and the allocation of the participant stipend. These data will be saved on a restricted file of the WHI secure Cleveland Clinic drive.

All study information will be maintained in a secure fashion as delineated by the Cleveland Clinic IRB: either in a locked cabinet in the OB/GYN and Women's Health Institute or on a secure WHI shared drive accessible only by IRB approved research team members.

Only members of the research team will have the ability to access this information. Access to research data will be restricted to members of the research team who are knowledgeable about applicable federal regulations and institution policies governing the involvement of human subjects in research.

Adverse Events and Data Monitoring:
The Principal Investigator will meet with the research team on a weekly basis to monitor progress of the study and reassess the human subject protection procedures, subject eligibility, and data collection strategies.

Based on our prior research, we do not expect any major adverse events or unanticipated problems related to the subject safety.

The PI will monitor subject safety throughout the course of the study, and promptly communicate any unanticipated problems to the IRB and the NEST DSMB as this is part of the NEST protocol.

Data Transfer Plan

1. All surveys (OBP, NEST, QBASE, QPV, QTT and QFF) completed by MetroHealth will be done either on a CCF/IRB approved iPad or via a direct email link that will take the participant directly to REDCap and will be stored via the Cleveland Clinic REDCap database. Study participant documentation will be stored and maintained by MetroHealth and CCF
2. MetroHealth will use the same, CCF/IRB approved, audio recording devices and will store the audio on their secure drive for data storage in the same manner as CCF.
3. Once a weeks, a member of the CCF study staff will travel to MetroHealth. During this visit, the audio files on MetroHealth secure drive will be transferred via an encrypted jump drive provided by CCF to a CCF laptop. During this visit, **we will also obtain electronic copies of signed informed consents for all newly enrolled MetroHealth participants (OB providers, patients and partners) at that time.**
4. MetroHealth will only have CCF REDCap access to input data and see data via their user group. All other REDCap functions will be disabled.

CCF Procedures

Initial Provider Recruitment

1. Research coordinator will send an IRB approved recruitment letter to providers who meet inclusion criteria
    a. Dr. Farrell, study P.I., will send follow up emails to providers
2. Distribute the OBP survey electronically through REDCap on CCF/IRB approved iPads

Initial Patient Recruitment

1. Chart review
2. Initial contact via MyChart or by email if sent through EPIC pool to patients who meet inclusion criteria
3. Obtain informed consent
    a. If consented into direct observation: provide CCF/IRB approved audio recorder, once completed the file is immediately stored on secure drive for data storage
4. Distribute the initial survey(s) electronically through REDCap on CCF/IRB approved iPads

Initial Partner Recruitment

1. Partner will be offered enrollment with consent of patient on day of 1st OB visit if partner arrives with the patient.
2. Obtain informed consent
    a. If consented into direct observation: provide CCF/ IRB approved audio recorder, once completed the file is immediately stored on secure drive for data storage
    b. Collect SSN, DOB and email for follow-up survey
3. Distribute the initial survey(s) electronically through REDCap on CCF/IRB approved iPads

Patient Follow-up(s)

1. Chart review, to be done prior to any communication
2. Send follow up surveys based on timeline:
    a. QPV: 7-9 days after first OB appointment
    b. QTT: 12-22 weeks of pregnancy (based on LMP)
    c. QFF: 22-24 weeks of pregnancy (based on LMP)

Partner Follow-up

1. If patient's Chart review is viable use the email given with consent to send QPV 7-9 days after first OB appointment.

MetroHealth Procedures

Initial Provider Recruitment

1. Research coordinator will send an IRB approved recruitment letter to providers who meet inclusion criteria
    a. Dr. Ranzini, site P.I., will send follow up emails to providers
2. Distribute the OBP survey electronically through REDCap on CCF/IRB approved iPads

Initial Patient Recruitment

1. Chart review
2. Initial contact via MyChart or by text message or by email if prompted through phone scheduler questionnaire to patients who meet inclusion criteria
3. Obtain informed consent
    a. If consented into direct observation: provide CCF/IRB approved audio recorder, once completed the file is immediately stored on secure drive for data storage to be collected by CCF
4. Distribute the initial survey(s) electronically through REDCap on CCF/IRB approved iPads

Initial Partner Recruitment

1. Partner will be offered enrollment with consent of patient on day of 1st OB visit if partner arrives with the patient.
2. Obtain informed consent
    a. If consented into direct observation: provide CCF/ IRB approved audio recorder, once completed the file is immediately stored on secure drive for data storage to be collected by CCF
    b. Collect SSN, DOB and email for follow-up survey
3. Distribute the initial survey(s) electronically through REDCap on CCF/IRB approved iPads

Patient Follow-up(s)

1. Chart review, to be done prior to any communication
2. Send follow up surveys based on timeline:
    a. QPV: 7-9 days after first OB appointment
    b. QTT: 12-22 weeks of pregnancy (based on LMP)
    c. QFF: 22-24 weeks of pregnancy (based on LMP)

Partner Follow-up

1. If patient's Chart review is viable use the email given with consent to send QPV 7-9 days after first OB appointment.

CCF Procedures

Audio transcriptions will be completed by the NEST study staff at CCF

All research stipends for patients (NEST [if applicable], QBASE, QPV, QTT & QFF) and partners (QBASE & QPV) will be sent through CCF

All gift cards for completion of the OBP survey (providers only) will be sent through CCF