

Expanded Prenatal Testing Options and Informed Choice (EPIC)

Trial Protocol

“Expanded Prenatal Testing Options and Informed Choice” (EPIC) is a randomized study of an “informed free choice” approach to prenatal testing among English- and Spanish-speakers of varying literacy levels. EPIC is an effectiveness trial -- pregnant women will be randomized to usual care (with no study intervention) or to the informed free choice approach to prenatal testing, in which they will view a Prenatal Testing Decision Support Guide for women of varying literacy levels and will be provided access to (and coverage for, if they don’t have insurance that pays for these tests) the first and second trimester screening and/or invasive diagnostic testing options they choose to undergo. The primary goal of the study is to assess the impact of the informed free choice approach to prenatal testing on the use of invasive diagnostic testing; secondary goals included assessing the impact of this approach on use of screening tests, on patient knowledge about prenatal testing and the conditions it tests for and risk comprehension, and on decisional conflict and regret. Participants will be recruited from the University of San Francisco, California); San Francisco General Hospital; Kaiser San Francisco, Oakland and Richmond; Santa Clara Valley Medical Center; Alameda County Medical Center; and La Clinica de la Raza, which together serve a diverse population of English- or Spanish-speaking women with varying literacy levels.

HYPOTHESES

Our hypotheses focus on three domains: invasive test use and testing strategy (including no testing), knowledge and risk comprehension, decisional conflict and regret. We posit that all domains will be affected by viewing the Prenatal Testing Decision Support Guide and having access to and coverage for the first and second trimester screening and/or diagnostic testing options discussed (the “informed free choice” approach).

Our primary hypothesis is that, compared to women who are randomized to usual care, women randomized to informed free choice will:

H1: Undergo invasive diagnostic testing at a lower rate.

Our secondary hypotheses are that, compared to women who are randomized to usual care, women who are randomized to informed free choice will:

H2: Be more likely to forego testing altogether;

H3: Have greater knowledge about prenatal testing;

H4: Have more awareness of prenatal testing procedure-related miscarriage risks and the chance that they are carrying a fetus with Trisomy 21; and

H5: Experience less decisional conflict and decision regret related to their prenatal testing decisions.

SUMMARY OF RELEVANT BACKGROUND AND PRIOR STUDIES

Background. Chromosomal disorders are the most common cause of congenital defects, and prenatal testing for these conditions has been a mainstay of obstetric care for over thirty years.

What began as an effort to decrease the incidence of Down-syndrome-affected births among women aged 35 and older² has expanded to include 1st and 2nd trimester screening efforts to identify women of all ages who are at increased risk for carrying an affected fetus. As a result, what historically was a relatively straightforward choice between having or foregoing amniocentesis for women who would be at least 35 at the time of their delivery has expanded to include decisions between multiple 1st and 2nd trimester screening and diagnostic tests that can be used alone or in various combinations by women of all ages. In 2007 the American College of Obstetricians and Gynecologists (ACOG) released new guidelines regarding screening³ and invasive diagnostic testing⁴ for fetal chromosomal anomalies, which emphasized that these tests should be made available to pregnant women of all ages. As part of this recommendation, ACOG emphasized that obstetric providers should “provide information about the detection and false-positive rates, advantages, disadvantages, and limitations, as well as the risks and benefits of diagnostic procedures” so that their patients can make informed decisions. The time and effort required to adequately explain all the options, however, presents a clear challenge to obstetric providers. Moreover, the difficulty of implementing the ACOG guidelines and recommendations is likely to be even more pronounced for lower literacy patients, particularly those whose primary language is not English.

Our prior studies of prenatal testing decision making. Our early research into prenatal testing decision making demonstrated dramatic racial/ethnic differences in the use of prenatal diagnostic testing for chromosomal disorders.⁵ More recently, we have found that racial/ethnic and socioeconomic differences in prenatal test use are mediated by faith and fatalism, value of testing information, and perceived risk of miscarriage,⁶ and that that Spanish-speaking Latinas often have misconceptions about prenatal testing and its goals.⁷ We also have collected preference data from over 1,000 sociodemographically diverse English-, Spanish-, and Mandarin- or Cantonese-speakers, and shown that patient values and preferences vary across racial/ethnic groups⁸ and are reflective of the social and familial context of testing,⁹ predictive of subsequent testing behaviors,⁶ and can project demand for testing services.¹⁰ In addition, we have used our preference data in the conduct of decision¹¹ and cost-effectiveness analyses;¹² we have described the determinants of perceived versus actual risks of procedure-related miscarriage and Down-syndrome-affected birth;¹³ and we have analyzed attitudes regarding pregnancy termination among a diverse cohort of pregnant women.¹⁴ We also have conducted an analysis of the history of and rationales for prenatal testing guidelines,¹⁵ provided evidence that women do not, on average, weight the outcomes of procedure-related miscarriage and Down-syndrome-affected birth equally,^{16 17} (calling into question part of the rationale for risk-based guidelines) and reviewed the evidence in support of our recommendation that women of all ages and risk levels should have the option of undergoing prenatal screening and/or invasive testing.¹⁸ We also have published recommendations for helping patients make informed decisions¹⁹ and methodological work in preference and socioeconomic status measurement in this context.^{17, 20, 21}

Decision aids and informed prenatal testing decision making. Decision aids have been developed²² and their use has been encouraged²³ to help patients and providers share in making informed decisions, particularly in situations that include more than one approach to care, uncertain outcomes, and benefits and harms that people value differently. In the area of prenatal testing, investigators in the United Kingdom,^{24, 25} Canada²⁶ and Australia²⁷ have

developed booklets, pamphlets and touch screen systems to help women make informed testing decisions. Several years ago, our group created and evaluated a prenatal testing decision assisting tool (PT Tool). The tool is a text-heavy computer program that presents detailed written information (with no audio component) about prenatal testing options, including the differences between screening and diagnostic tests and their test performance characteristics, and the conditions for which they test. It provides individualized risk assessments using a “wall of balls” format, and emphasizes the importance of patient values and preferences in making informed testing decisions. A series of values clarification exercises are used to guide users towards the prenatal testing strategies that may be the most appropriate for them, including foregoing testing altogether.

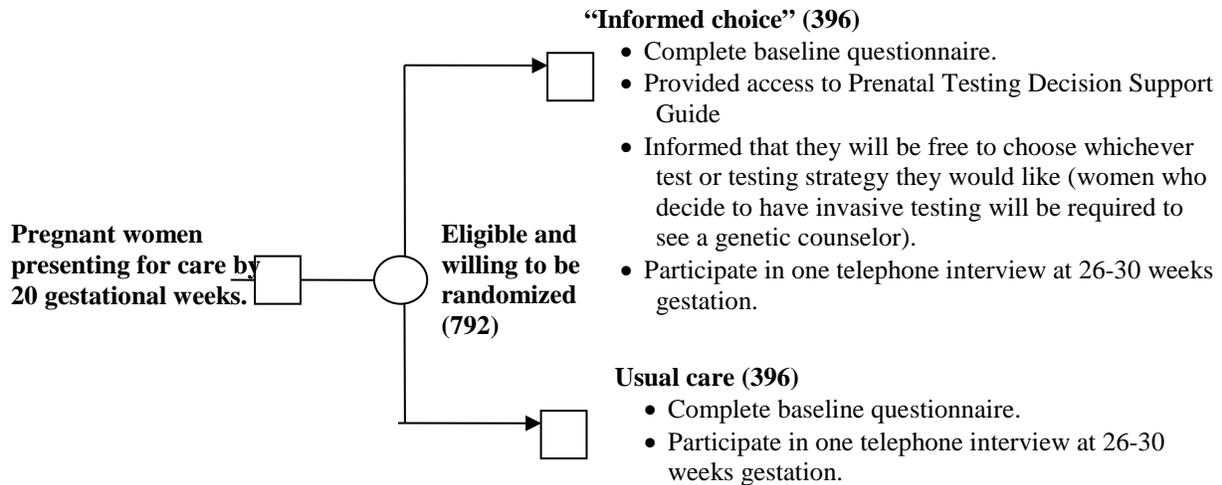
We evaluated the original PT Tool among 496 women, most of whom had attended college. We found that women randomized to PT Tool had higher knowledge scores (79.5% versus 64.9%, $p < .001$), were more likely to correctly estimate their risk of procedure-related miscarriage (64.9% versus 48.1%, $p = .002$) and carrying a Down syndrome-affected fetus (63.5% versus 15.1%, $p < .001$), were more satisfied with the intervention ($p < .001$), and had less decision uncertainty ($p < .001$) than controls. Among women aged 35 and older, PT Tool viewers who were originally *less* inclined to undergo invasive testing were ultimately more likely than similarly inclined controls to have amniocentesis or chorionic villus sampling (44.8% versus 29.2%), while those who were originally *more* inclined to undergo an invasive procedure ultimately were less likely than similarly inclined controls to have a diagnostic procedure (84.6% versus 94.9%; $p = .015$ for interaction). This increased deviation from original inclination among PT Tool viewers, which was accompanied by greater knowledge and less decisional conflict, led us to conclude that the original PT Tool helps higher literacy women make more informed prenatal testing decisions, and that decision tool should be made available to women of all ages and literacy levels to help them make informed prenatal testing decisions.¹

Since developing PT Tool, a number of new screening options have emerged, and the need to create tools that can be used by women of varying literacy levels has become increasingly apparent. We therefore used the general structure of the original tool to create a more comprehensive “Prenatal Testing Decision Support Guide” which includes the more recent 1st trimester screening options and is designed for use by women of lower literacy levels. The guide is also an interactive computer program, but rather than relying on written text it is a dynamic program that the user views, listens to, and interacts with, and is narrated by a local African American newscaster using pictures and graphics to convey key concepts. Prior to creating the Prenatal Testing Decision Support Guide we conducted numerous focus groups with women enrolled in Adult Literacy “Learner” groups, where we pilot tested segments and used the results to design a draft version of the guide. We then pre-tested the draft guide and conducted numerous cognitive debriefings with lower literacy English speakers, who found it generally acceptable and easy to understand, but suggested further changes. We incorporated the suggestions into the final version, which meets the criteria set by the International Patient Decision Aid Standards (IPDAS) Collaboration.²⁸

STUDY DESIGN

We will perform an open, parallel-comparison randomized clinical trial of an “informed free choice” approach to prenatal testing compared to usual care among 792 English- or Spanish-speaking women presenting for prenatal care prior to 20 completed gestational weeks.

Study Schematic



396 women will be randomized to usual care, the control group, in which they will receive no intervention beyond a baseline pre-randomization interview and one follow-up telephone interview. The other 396 women will be randomized to “informed free choice,” in which they will be provided access to the Prenatal Testing Decision Support Guide and will be told that they can have whatever tests they would like to undergo, and that tests for which they do not have coverage will be paid for by the study. (Medi-Cal and most insurance companies will cover first trimester screening (both nuchal translucency ultrasound and biochemistry) or second trimester screening for women of all ages and CVS or amniocentesis for women aged ≥ 35 or who have otherwise screened positive. The State of California’s Expanded AFP Program covers amniocenteses for women who have screened positive on an expanded AFP test. We therefore anticipate needing to pay for a few of the 1st trimester screening tests and a smaller number of invasive diagnostic tests that women who have not screened positive and who are less than 35 may elect to undergo.) Women randomized to informed free choice also will participate in the follow-up telephone interview.

Participants and Patient Flow

Sources of participants. Participants will be recruited from the University of San Francisco, California (UCSF); San Francisco General Hospital (SFGH); Kaiser San Francisco, Oakland and Richmond; Santa Clara Valley Medical Center; Alameda County Medical Center; and La Clinica de la Raza.

Eligibility criteria. Eligibility criteria for this study include:

- Ability to speak English or Spanish
- Presentation for prenatal care before the 20th week of pregnancy
- Singleton or twin gestation
- Not yet having undergone any prenatal testing for fetal aneuploidy in the current pregnancy

Limiting the language to English or Spanish will eliminate some women from participating in the study. However women who read and understand these languages constitute the majority of the patients seen at the recruitments sites, and translating the tool into all other languages spoken is beyond the scope of this effort. We have chosen the eligibility criteria of presentation before the 20th week, since those women who seek care at this point are still early enough to have at least one prenatal testing option remaining and we are interested in capturing the decision making of all women who still have a prenatal testing option.

Recruitment process. Given the relatively early gestational deadlines for 1st trimester screening and diagnostic options, early and efficient recruitment will be critical to allow patient contact prior to their undergoing any screening or diagnostic testing procedures. We will use a two-tiered approach to ensuring that potential participants are aware of the study early in their care.

In the first tier of the recruitment, a study interviewer, who will have access to appointment schedules, will send letters on behalf of the local clinician describing the study to patients who have new obstetric appointments. The letter will be written at the fifth-grade level, and will include an “opt in/opt out” card, which the participant can mail back. Patients who return the “opt in” card will be contacted by an interviewer to discuss the study with them and assess their eligibility and interest in participating. If a potential participant does not return the opt-out card within one week, the research associate will call by telephone to ask whether she is interested in hearing about the study. If a telephone message does not result in a return phone call within a second week, another attempt will be made to reach the potential participant by telephone. This relatively short interval is important to allow contact with potential participants early in pregnancy, before prenatal testing decisions have been made, and/or tests performed. If contact is not established, no further attempts will be made. If contact is established, the research associate will explain the study and determine eligibility, and ask whether the woman is interested in participating. Baseline interviews will be scheduled with all eligible and interested participants as soon as possible after the initial contact.

In the second tier, women presenting for prenatal care prior to 20 completed gestational weeks will be told about the study by their prenatal care provider (perinatal nurse, nurse midwife, or obstetrician) during their first prenatal visit. Written information on the study will be included in the information packet given routinely to new patients. (This packet also contains information about prenatal testing options which is reviewed with the patient by the provider.) If the woman indicates an interest in participating in or hearing more about the study, she will be asked to complete an opt in card so she can be contacted as soon as possible.

Study interviewers will be available by phone to describe the study and schedule appointments for study enrollment interviews at the participant’s convenience. Because the second tier of

recruitment will take place in a setting where testing is already being discussed, and study participation will be offered to all women presenting for care by 20 gestational weeks, we expect that providers will readily incorporate a brief discussion of the study into their routine care.

This protocol, which has been approved by Institutional Review Boards at all the participating sites, will help ensure a voluntary and timely enrollment. Our goal is to recruit 792 participants over an 18-month period (about 44 per month).

Patient flow. At the beginning of the face-to-face interview, each participant will be asked to provide informed consent and then to complete a baseline questionnaire which will be administered by the interviewer. She will then be randomized to informed free choice or usual care. Each participant who is randomized to informed free choice will be provided access to the Prenatal Testing Decision Support Guide and told that after she views the tool she will be free to meet with a genetic counselor or to choose whatever tests she prefers, and that the study will pay for the genetic counselor and any tests that for which she does not have coverage. Women randomized to usual care will have no study-initiated intervention. Usual care may vary somewhat by practitioner and site, but essentially includes written materials and a brief review of options available based on maternal and gestational age and referral of women aged ≥ 35 to a genetic counselor. All women will receive \$40 as remuneration for the face-to-face interview. All women will receive a follow-up telephone call after completing their 24th gestational week (and prior to their 36th gestational week), after all prenatal testing decisions will have been made. These women will be mailed a \$40 gift card after completing the telephone interview.

Variables and Measures

Predictor variable and covariates. The primary predictor for all outcomes will be the randomization assignment. We also will measure, before randomization, a set of covariates that may act as predictors or moderators of the effects of the primary predictor. Most items for measuring these variables are based on published validated measures. They include sociodemographic characteristics, questions pertaining to the participant's reproductive history and current pregnancy, familiarity with Down syndrome and other genetic conditions, attitudes and beliefs,⁶ social norms (based on the work of Gaither and colleagues³⁷), pregnancy worries,³⁸ depression (as assessed by the Prime-MD PHQ Depression Questionnaire^{39,40}), numeracy,⁴¹ and literacy (using the Spanish version of the Short Test of Functional Literacy in Adults; S-TOFHLA⁴²).

Outcome variables. Our primary outcomes relate to our hypotheses and include prenatal test utilization, knowledge about prenatal testing and birth defects, risk comprehension, and decisional conflict and decision regret.

- We will assess **utilization of prenatal screening and diagnostic tests** via review of medical records.
- To assess **knowledge**, we will employ a 15-item scale we developed using 4 items from the Maternal Serum Screening Knowledge Questionnaire⁴³ and 11 new items which were derived from an exploratory factor analysis of a larger pool of eight items in our

previous study of prenatal testing decision making in over 1,000 racially/ethnically and socioeconomically diverse women.^{9,44} Cronbach's alpha for that measure is 0.80, and the scores are highly correlated with education level ($r=0.53$, $p<0.0001$).

- **Risk awareness and comprehension** will be assessed by asking patients to choose between one of several risk categories for procedure-related miscarriage and Down-syndrome affected fetus.
- We will measure **decisional conflict** using our modification of the Decisional Conflict Scale,³¹ which has demonstrated good item reliability in our prior studies (0.84; 0.86). **Decision regret** will be measured using a 3-item scale we developed for our prior studies.

Timing of Measures

	Baseline face-to-face interview	Telephone follow up interview	Record review
Sociodemographics	X		
Parity, reproductive and prenatal testing history	X		
Familiarity with Down syndrome and other genetic conditions	X	X	
Attitudes and beliefs about pregnancy, disabilities, risk miscarriage and abortion	X	X	
Social norms	X		
Pregnancy worries	X	X	
Depression	X	X	
Numeracy	X		
Literacy	X		
Prenatal test utilization		X	X
Knowledge about prenatal testing and birth defects		X	
Risk awareness and comprehension		X	
Decisional conflict		X	
Decision regret		X	

Analyses Plan

Sample size estimates.

Our primary hypothesis is that women who are randomized to informed free choice will undergo invasive prenatal diagnostic testing at a lower rate than women randomized to the usual care group, regardless of maternal age. Given that the restrictions on access to testing based upon maternal age have been eliminated, we hypothesize that women of all ages who are randomized to informed free choice will have lower invasive test use rates compared to women randomized to usual care. In our study of trends in the use of invasive diagnostic testing among women who delivered at an integrated health care system in California, we found that the number of amniocenteses and CVS procedures

performed as a percentage of the total number of deliveries in 2006 was 12.1%. Assuming 80% power, two-tailed alpha equal to 0.05, 90% retention at follow-up, and a 12.1% invasive test use rate within the usual care group, a sample size of 792 will be capable of detecting a group difference corresponding to an invasive test use rate of $\leq 6.2\%$ in the informed free choice group (OR=2.10, a 'small-medium' effect size). We also hypothesize that compared to usual care, women in informed free choice will have increased testing knowledge and risk comprehension as well as reduced decisional conflict and decision regret; the design is capable of a minimum detectable a group difference equal to $d=0.21$ standard deviations, which is considered a 'small' effect size.

Primary Analyses

Cross-sectional and descriptive analyses. Cross-sectional analyses will be similar for the baseline and each follow-up survey. First, we will conduct descriptive analyses to profile the sample, including examination of means and proportions, measures of variability, and confidence intervals around these statistics. Statistics will be calculated for each intervention group, site, and age stratum. Examination of univariate distributions may prompt normalizing transformations where such transformations are defensible and are a component of the best available analysis strategy. We will investigate bivariate relationships within and between measurement domains (e.g. demographics, outcomes).

Assessment of primary and secondary outcomes. Effects of the intervention on use of invasive testing, testing strategy undergone, knowledge, risk awareness and comprehension, decisional conflict, and decision regret will be estimated with logistic and linear regression models, as appropriate. In addition to testing the group main effect, the models will also include explanatory variables indexing maternal age strata and recruitment site. Intervention effects on participants' invasive testing utilization will be tested with logistic regression models. A logistic regression model will test the main effect of intervention groups, age strata, and their interaction.

Tests of moderation. These analyses will further elaborate any observed treatment effects by helping to determine whether demographic strata, attitudes and beliefs, and prior experiences moderate any treatment effects. Each outcome will be regressed onto measures of study site, race/ethnicity, language preference, literacy (adequate versus less than adequate), parity, prior exposure to genetic counseling, and their interactions with age strata and intervention group assignment. In these models, a significant interaction term suggests that the treatment effect is moderated by the corresponding interacting variable.

Additional Modeling Considerations

Randomization check. A randomization check will determine whether intervention group assignment is independent of outcome and covariate measures assessed at baseline. In the event that randomization fails to establish equivalent groups at baseline, we will modify group comparisons to include a quintile-stratified propensity adjustment, which can significantly reduce bias under such circumstances.⁵¹⁻⁵³ Propensity scores will be estimated by regressing the intervention group indicator onto baseline indicators of demographics and covariates. Next, individual propensity score estimates will be grouped into quintiles and the propensity quintile-by-groups cross-classification will be inspected to insure that each cell is adequately represented. Regression models testing intervention group differences will initially include a

quintile-by-groups interaction term to test whether the intervention effect is equivalent across propensity quintiles. A significant interaction term would suggest quintile-specific treatment effects, which would then be estimated and reported. A non-significant interaction term would suggest equivalent intervention effects across propensity quintiles; the interaction term would be removed from the model, and the intervention effect estimated conditional on the propensity-quintile main effect.

Missing data. Although protocols have been designed to promote retention, some attrition is inevitable. We will perform analyses to help determine whether differential attrition occurred between intervention groups, sites, age groups, and socioeconomic strata. These analyses will include (1) a breakdown of the frequency of reasons for attrition in each group (e.g. refusal, moved, deceased); (2) comparisons of key baseline measures between those who dropped out of the study versus those who did not; and (3) a comparison of attrition rates across intervention groups and principal demographic strata. Although case-wise deletion provides a conservative basis for sample size estimation, it and other ad hoc approaches to handling missing data will not be used for analysis. Generally, ad hoc procedures require that the data are missing completely at random (MCAR)⁵⁴ to obtain unbiased parameter estimates and also entail a loss of statistical power resulting from discarded cases. Instead, multiple imputation^{55, 56} will be used, which invokes the relatively mild assumption that the data are missing at random (MAR).⁵⁴⁻⁵⁷

Randomization. Randomization will be stratified by age (< 35 v ≥ 35 years), recruitment site, parity (nulliparous v parous), and interviewer. Prior to initiation of the study, stratum-specific sequential ID numbers will be generated and randomly pre-assigned to intervention groups in blocks of 4. Only the PI will have access to the linkage between ID numbers and treatment assignments. Upon enrollment, each woman's stratum will be identified and the next sequential ID number from her stratum will be assigned. Although enrollment sequence will ultimately determine intervention assignment, the intervention assignment will not be revealed to the participant until after the baseline interview is complete. At that time, the study research assistant will open a sealed, opaque envelope pre-printed with the participant's ID number. Inside the envelope a card will (redundantly) list the participant's ID number and reveal her intervention group assignment.

Data management and confidentiality. Two databases will be created as part of this study. The first "participant tracking" database will contain all identifying information that will permit locating participants for their follow-up interviews, and will include all demographic information for all patients who do not meet the eligibility criteria or who decline participation, along with their reasons for refusal (to permit comparisons between those who do and do not enter the study). This database also will be used for scheduling participants and ensuring that all study tasks are completed on time. The second "study data" database will contain all project-related data used for the study analyses (e.g., questionnaire and interview data, randomization assignment, and chart review data). Participants will be identified only by a randomly generated code number in the study database. The third database will contain the key linking each subject's identifying information to a code number. Only the PI and a limited number of study staff will have access to this database which will be encrypted and stored on a secure university server.

Only code numbers will be used and no individual identities will be retained in the analysis or publications. Data will be entered by hand-key entry into a database designed with full error (logic and range) checking. A random 10% sample of questionnaires will be entered in duplicate to ensure accuracy of data entry. Confidentiality of data will be ensured by using only a coded participant acrostic and code number to identify respondents on the data-collection forms.

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