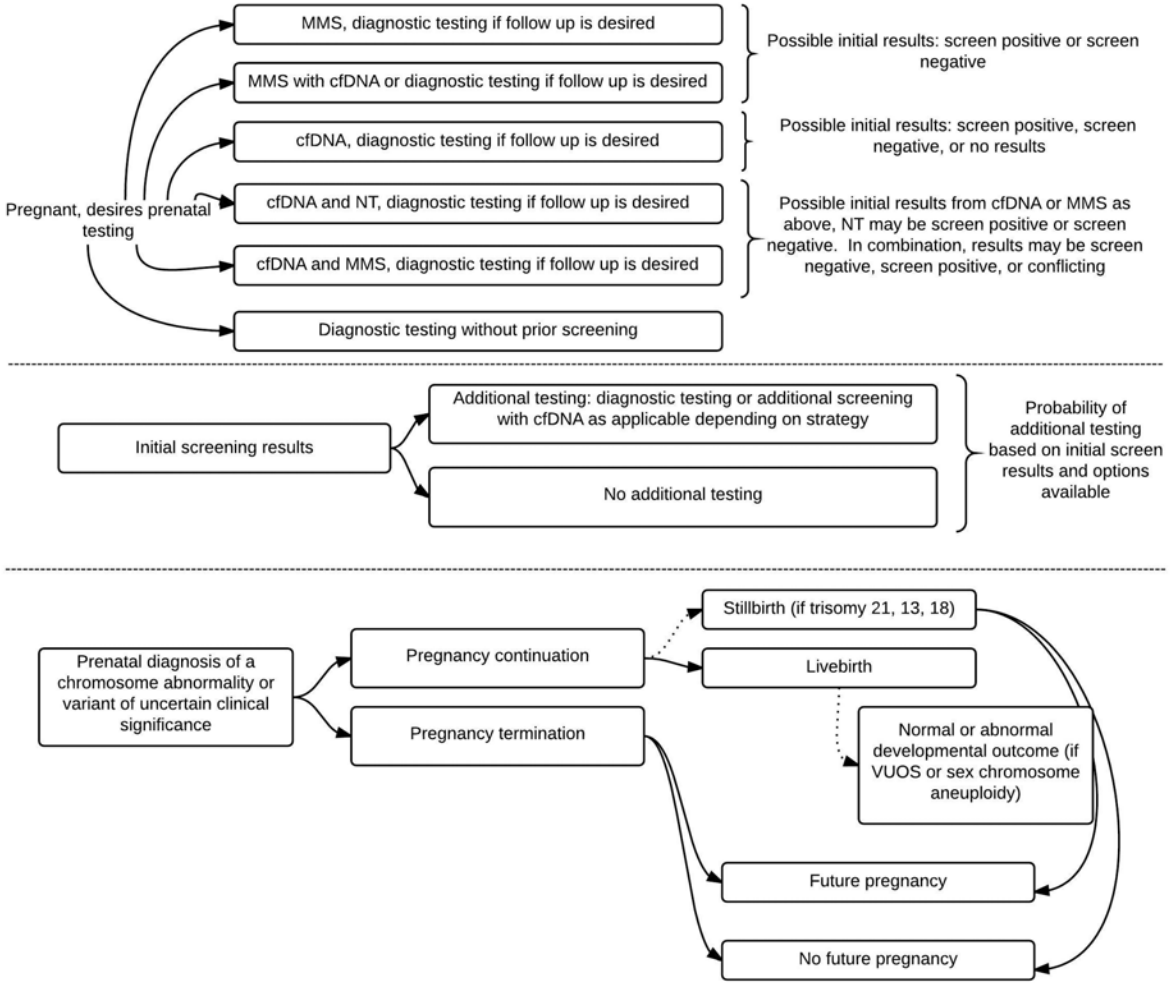
Appendix 1. Schematic representation of decision tree. Each initial screening test can yield positive or negative results, which may or may not be followed up with an additional test. No results from cell free DNA (cfDNA) screening are treated as screen positive results. The probability of follow-up testing is dependent on the results of the initial test and the options available for follow-up. Chromosomal abnormalities include trisomy 21, 13, 18, sex chromosome aneuploidy (XO, XXX, XXY, XYY), pathogenic copy number variant or rare chromosomal abnormalities, and variants of uncertain clinical significance. The possibility of stillbirth in the context of trisomy 21, 13 or 18 is included. Diagnostic testing may result in miscarriage. Receipt of abnormal results or results indicating a variant of uncertain significance may result in a decision to continue or to terminate a pregnancy. The probability of a future pregnancy in the context of a pregnancy loss is also included. MMS, multiple marker screening; NT, nuchal translucency; VUOS, variants of uncertain clinical significance.



Appendix 2. Probabilities and Costs Used in the Analysis

Probabilities		Reference
Age independent probabilities		
Probability of clinically significant microarray abnormality or rare chromosomal abnormality	0.0114	[1,2]
Probability of variant of unknown clinical significance	0.013	[1]
Age dependent probabilities		
Age 20		
Trisomy 13	0.0001	[12-18]
Trisomy 18	0.0002	[12-18]
Trisomy 21	0.0008	[12-18]
Sex chromosome aneuploidy (XXX, XXY, XYY, XO)	0.0034	[12-18]
Age 25		
Trisomy 13	0.0001	[12-18]
Trisomy 18	0.0002	[12-18]
Trisomy 21	0.001	[12-18]
Sex chromosome aneuploidy (XXX, XXY, XYY, XO)	0.0034	[12-18]
Age 30		
Trisomy 13	0.0002	[12-18]
Trisomy 18	0.0004	[12-18]

Trisomy 21	0.0014	[12-18]
Sex chromosome aneuploidy (XXX, XXY, XYY, XO)	0.0034	[12-18]
Age 35		
Trisomy 13	0.0004	[12-18]
Trisomy 18	0.0009	[12-18]
Trisomy 21	0.0034	[12-18]
Sex chromosome aneuploidy (XXX, XXY, XYY, XO)	0.0035	[12-18]
Age 40		
Trisomy 13	0.0014	[12-18]
Trisomy 18	0.003	[12-18]
Trisomy 21	0.0116	[12-18]
Sex chromosome aneuploidy (XXX, XXY, XYY, XO)	0.0051	[12-18]
Test characteristics		
Multiple marker screening (NT+1st and 2nd trimester serum samples)		
Age independent test characteristics		
Sensitivity of MMS for trisomy 13	0.804	[3]
Sensitivity of MMS for microarray or other rare chromosomal abnormalities	0.538	[3]
Sensitivity of MMS for variant of uncertain clinical significance	0.538	[3]
Sensitivity of MMS for sex chromosome aneuploidy	0.627	[3]

Age 20		
Sensitivity of MMS for trisomy 18	0.68	[4]
Sensitivity of MMS for trisomy 21	0.81	[4]
Screen positive rate	0.021	[4]
Age 25		
Sensitivity of MMS for trisomy 18	0.70	[4]
Sensitivity of MMS for trisomy 21	0.82	[4]
Screen positive rate	0.021	[4]
Age 30		
Sensitivity of MMS for trisomy 18	0.074	[4]
Sensitivity of MMS for trisomy 21	0.084	[4]
Screen positive rate	0.032	[4]
Age 35		
Sensitivity of MMS for trisomy 18	0.84	[4]
Sensitivity of MMS for trisomy 21	0.91	[4]
Screen positive rate	0.085	[4]
Age 40		
Sensitivity of MMS for trisomy 18	0.93	[4]
Sensitivity of MMS for trisomy 21	0.96	[4]

Screen positive rate	0.23	[4]
Cell free DNA testing (cfDNA)		
Failed test (no results returned)		
Probability of failed cfDNA when sex chromosome aneuploidy is present	0.0714	[5]
Probability of failed cfDNA when trisomy 13 is present	0.152	[6–9]
Probability of failed cfDNA when trisomy 18 is present	0.105	[6-9]
Probability of failed cfDNA when trisomy 21 is present	0.044	[6-9]
Probability of failed cfDNA in the absence of aneuploidy	0.04	[6-9]
cf DNA test characteristics when a result is returned		
Sensitivity of cfDNA for trisomy 13	0.921	[10]
Sensitivity of cfDNA for trisomy 18	0.968	[10]
Sensitivity of cfDNA for trisomy 21	0.99	[10]
Sensitivity of cfDNA for sex chromosome aneuploidy	0.9114	[10]
False positive rate for cfDNA	0.0067	[10]
Nuchal translucency (NT)		
Sensitivity of NT for sex chromosome aneuploidy	0.435	[11, 12]
Sensitivity of NT for variant of uncertain clinical significance	0.398	[11, 12]
Sensitivity of NT for trisomy 21	0.587	[11, 12]
Sensitivity of NT for trisomy 18	0.618	[11, 12]

Sensitivity of NT for trisomy 13	0.586	[11, 12]
Sensitivity of NT for rare chromosomal abnormalities	0.398	[11, 12]
Screen positive rate of NT	0.05	[11, 12]
Diagnostic testing		
Sensitivity of amniocentesis for detection of chromosomal abnormalities	0.998	[13,14]
Probability of additional testing		
Probability of diagnostic testing with a negative screening test	0.044	[15]
Probability of diagnostic testing after positive MMS when cfDNA is available	0.392	[15]
Probability of diagnostic testing with 2 positive screening tests	0.776	[16]
Probability of cfDNA testing after positive MMS	0.394	[15]
Probability of diagnostic testing after positive MMS when cfDNA is not available	0.776	[16]
Probability of diagnostic testing after negative cfDNA	0.044	Assumption, same as screen positive prior to cfDNA available
Probability of diagnostic testing after cfDNA positive for trisomy	0.776	Assumption, same as screen positive prior to cfDNA available
Probability of diagnostic testing after cfDNA positive for sex chromosome aneuploidy	0.5	Assumption
Probability of diagnostic testing after failed cfDNA	0.776	Assumption, same as screen

		positive prior to cfDNA available
Probability of termination		
Probability of termination for trisomy 13	0.648	[17–19]
Probability o termination for trisomy 18	0.598	[17–19]
Probability of termination for trisomy 21	0.742	[20]
Probability of termination for microarray or rare chromosome abnormality	0.742	Assumption, same as trisomy 21
Probability of termination for variant of uncertain clinical significance	0.325	Assumption, same as sex chromosome aneuploidy
Probability of termination for sex chromsome aneuploidy	0.325	[21,22]
Probability of miscarriage		
Probability of procedure-related loss	0.0025	[23]
Probability of spontaneous loss with trisomy 13	0.42	[24]
Probability of spontaneous loss with trisomy 18	0.72	[24]
Probability of spontaneous loss with trisomy 21	0.043	[25]
Probability of intellectual disability		
Probability of intellectual disability in the setting of sex chromosome aneuploidy	0.3	Assumption
Probability of intellectual disability with variant of uncertain clinical significance	0.5	Assumption

Probability of future birth after pregnancy loss		
Age 30 and younger	0.75	[26,27]
Age 35	0.66	[27]
Age 40	0.44	[27]
Other		
Life expectancy at 20	61.6	Social Security Actuarial Tables[28]
Life expectancy at 25	56.8	Social Security Actuarial Tables[28]
Life expectancy at 30	51.9	Social Security Actuarial Tables[28]
Life expectancy at 35	47.1	Social Security Actuarial Tables[28]
Life expectancy at 40	42.3	Social Security Actuarial Tables[28]
Life expectancy at 45	37.6	Social Security Actuarial Tables[28]
Discount rate	0.03	Assumption
Costs		

Serum portion of integrated screen	$338	Mean of quoted costs from major lab providers
Nuchal translucency ultrasound	$222	Mean of quoted costs for insured and Medicaid patients
Amniocentesis with CMA	$2384	Mean of quoted costs for insured and Medicaid patients
cfDNA	$1796	Mean of quoted costs from all cfDNA providers
Termination or miscarriage	$938	[29]
Delivery cost	$8445	[30]

Appendix 3. Utility Measurement Methods

We measured time tradeoff utilities for 18 different sequences of events that can follow 6 testing strategies beginning with 1) multiple marker testing (serum biochemistry and nuchal translucency ultrasound) alone, 2) cell free DNA analysis alone, 3) multiple marker screening and cell free DNA together, or 4) diagnostic testing with CMA, and 5 different outcomes of pregnancy (birth of an infant with an intellectual disability, birth of an infant with a severely life threatening condition, and birth of an infant following the identification of a variant of unknown significance, as well as pregnancy loss with or without the birth of an infant from a subsequent pregnancy).

Participants were recruited primarily from the Prenatal Diagnosis Center at the University of California, San Francisco (UCSF); secondary recruitment sites included the prenatal care clinics at UCSF and San Francisco General Hospital. After obtaining approval from the institutional review board for each site, participants were enrolled in the study between July, 2013, and November, 2014. Eligibility criteria included being at least 18 years old and less than 20 weeks pregnant, carrying a singleton pregnancy with no major fetal abnormalities, and having the ability to complete a 45 minute interview in English. Women were eligible to participate regardless of whether or not they had undergone any prenatal testing in their current pregnancy.

After signing informed consent, each participant was asked to complete a self-administered questionnaire, which contained items related to their sociodemographic characteristics, reproductive history, and prior use of prenatal testing. We then providing participants with information on the conditions (intellectual disability (including, but

not limited to, Down syndrome), trisomies 13 and 18, and a genetic variant of uncertain or variable clinical significance) and testing options (multiple marker screening, cell free DNA, and CVS and amniocentesis with CMA) for which utilities were sought. The description of multiple marker screening included first and second trimester blood draw as well as nuchal translucency ultrasound, a sequential integrated screening approach.

We employed a 3-form design to minimize responder burden.[31] All participants assessed the 5 pregnancy outcome scenarios first. The other 18 scenarios were divided into 3 groups (6 scenarios in each), and each participant was randomly assigned to evaluate 2 of the 3 groups of pregnancy scenarios. Each scenario was read aloud by the study interviewer, while the participant viewed a card with the written description and a graphic representation of the sequence of events described. The back of the card listed emotions that might occur as a result of experiencing the scenario, to help the participants consider how they might feel about being in the situation described. After completing the interview, each participant was given a $40 gift card as remuneration.

Sociodemographic characteristics of the study population are included as Appendix 4. Just over half (55.2%) of the sample self identified as white; the remainder were Asian (22.4%), Latina (13.2%) and African American (7.8%). They ranged in age from 18 to 46; the mean age was 33.4 (±4.8). These women varied substantially in their reproductive histories: about a third (32.0%) had previously given birth, 28.5% had experienced a miscarriage, and 22.8% reported having terminated a pregnancy.

Appendix 4. Utility Measurement Participant Characteristics (n=281)

Sociodemographic characteristics	**n**	**%***
Race/ethnicity		
African American or Black	22	7.8%
Asian	63	22.4%
Latina, Latin American or Hispanic	37	13.2%
White	155	55.2%
Mixed, other	4	0.5%
Age		
18-24	10	3.3%
25-29	45	16.0%
30-34	122	43.4%
35-39	70	24.9%
≥40	34	12.1%
Education attainment		
High school graduate or less	12	4.2%
Some college	37	13.2%
College graduate	90	32.0%
Professional or graduate degree	142	50.5%

Income		
< $25,000	32	11.7%
$25,000 - $50,000	25	9.2%
$50,001 - $100,000	41	15.0%
$100,001 - $150,000	68	24.9%
Over $150,000	107	39.2%
Private insurance	219	78.2%
Married or living with partner	249	88.6%
Personally know someone with intellectual disability	191	69.2%
Reproductive history		
Prior birth	190	32.1%
Prior miscarriage	80	28.6%
Prior termination	64	22.9%
Have met with genetic counselor in current pregnancy	235	83.9%
Have had prenatal testing in current pregnancy*	178	90.4%
Multiple marker screening	167	84.8%
cf DNA screening	37	18.8%
Chorionic villus sampling	5	2.5%
Amniocentesis	1	0.5%

*% out of 281; does not always add to 100% due to missing data.

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