Genetic Counseling Before and After PGD/S

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Disclosures

- Genetic Counseling Advisory Board Member for Good Start Genetics
- Speaker's Bureau for Illumina
- Business Development Team Member for InformedDNA

Learning Objectives

- Outline various approaches for genetic counseling and informed consent for PGD/S prior to testing
- Understand the differences between the various prenatal testing options after PGD/S
- Gain skills to support patient's prenatal decision making after PGD/S

Who can provide informed consent?

- Physician
- Nurse
- Genetic Counselor
- Embryologist
- Other clinic support staff

Why might a genetic counselor best provide this service?

- Genetic counselor skill set –
  - **Genetic Risk Assessment –** family history review to discover if there are any patterns of genetic conditions in the family that may lead to additional testing for the patient (opportunity for patient education); documentation of inheritance patterns for PGD cases and identify family members' DNA samples needed for PGD set up
  - **Informed Consent Process –** discussion of methods, benefits, limitations, and potential risks of PGD/S
- Ability to explain methodology of PGD/s for optimal patient understanding
- Availability to patient for specialized and individual care
- Liaison between lab personnel, IVF clinic and the patient
- Keeping the IVF practice informed and up to date regarding genetics in general and specifics of PGD cases
- Medical Legal Issues – ensuring appropriate set up for PGD

How can a genetic counselor be incorporated into your practice?

- Employee
- Independent consultant
  - Provide service on site at clinic
  - Provide service remotely by telephone/webinar/video conferencing
- Referral to a genetic counselor that works at an outside genetics practice or PGD lab
- Referral to a telephone genetic counseling service

How can genetic counseling and informed consent be provided?

- Face to face consultation
- Telephone consultation
- Informational video with follow up discussion (face to face or telephone)
- Classroom style presentation with many patients with follow up individualized counseling/consenting

Genetic Risk Assessment

Genetic counseling provided for 691 unselected couples pursuing IVF - 65% (452) had identified risk

- 112 family history of mental retardation, Down syndrome or autism
- 75 had increased risk of cancer
- 23 carriers of cystic fibrosis
- 16 carriers of a hemoglobinopathy
- 5 carriers of Tay-Sachs
- 5 consanguineous
- 4 chromosome abnormality (self or previous child)

A.Vance, C.Zouves. "The Importance of Family History Risk Assessment in the Infertility Setting. *Fertility and Sterility.*" Volume 84, pg S125-S125

Essential Components of Informed Consent

- Benefits of PGD/S as reported in the literature and also based on clinic's data
- What kinds of results the clinic is willing to transfer (in additional to normal, perhaps aneuploidy, variants of uncertain significance, mosaic results, variable penetrance/expression conditions ,etc.)
- Alternatives to PGD for building a family
  - Spontaneous conception followed by pre- or postnatal diagnosis
  - Gamete donor
  - Adoption
- Limitations of PGD
  - What is detected and what is not tested
  - Accuracy of the testing, possibility of embryo mosaicism
  - Risks with IVF, embryo cryopreservation & embryo biopsy
  - Need for confirmatory prenatal testing

Benefits of PGD/S

- Aneuploidy screening (PGS)
  - Increased implantation rates*(1)
  - Increased ongoing pregnancy rates*(1)
  - Increased livebirth rates*(2)
  - Decreased miscarriage rates*(1)
  - Maintained pregnancy rates with eSET, decrease in multiple gestations(3)
  - Significantly reduced risk for aneuploidy in ongoing pregnancy (no longer at age related risk)
- Single gene testing (PGD)
  - All of the above benefits. PGS is now typically included with PGD
  - Significantly reduced risk of specific single gene disorder tested by PGD in the ongoing pregnancy

* Per embryo transferred compared to untested embryos

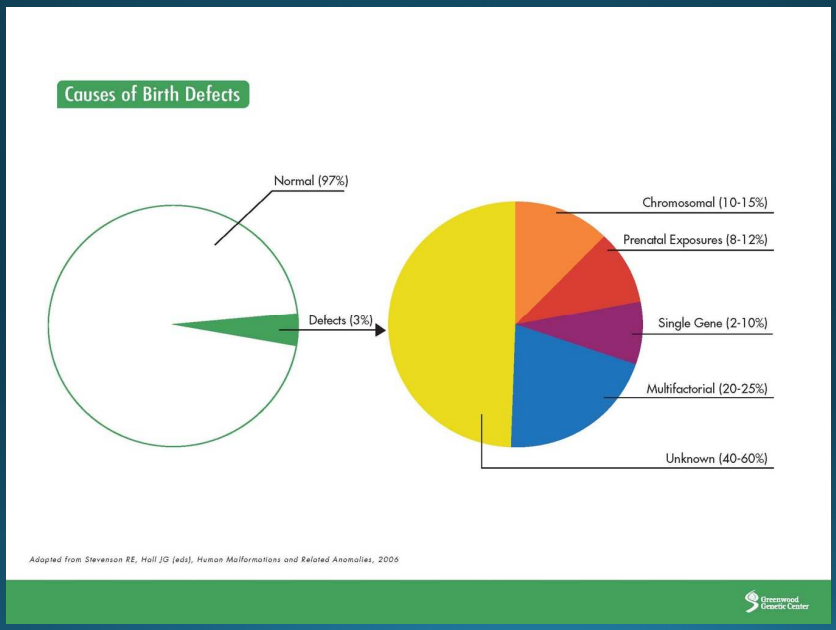
1 Young, good prognosis patients with PGS (day 5 biopsy/eSET) 65% relative increase in ongoing pregnancy rate (Yang et al, 2012 *Mol Cyto*) **2** Blastocyst biopsy with CCS and fresh embryo transfer (<43 years) CCS (qPCR) increases LB rates (Scott et al., 2013 *Fertil Steril*) **3** Single euploid blastocyst transfer with PGS is not inferior to two-blastocyst transfer (Forman et al 2013, *Fertil Steril*)

"Based on the large body of the collected data, there is now strong evidence that preimplantation aneuploidy testing is fast becoming one of the basic ART technologies required for selection of viable embryos for transfer and as a standard procedure in improving IVF outcomes."

Excerpt from 2015 PGDIS Statement on the Utility of Preimplantation Aneuploidy Testing in ART

Limitations for PGD/S

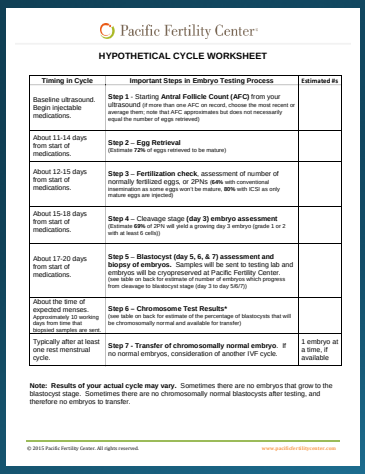
- Embryo testing does not afford 100% detection rate for aneuploidy or single gene mutation analysis
- Does not detection birth defects unrelated to aneuploidy or single gene disorder (i.e. spina bifida)
- Does not detect developmental or cognitive disability (i.e. autism)
- Does not detect multifactorial adult onset conditions (psychiatric disorder, diabetes, cancer, heart disease, etc.)
- Detection rate limited by possibility of mosaicism
- DOES NOT DETECT "EVERYTHING"



Additional limitations

- Will there be enough embryos that survive to biopsy?
- Will there be any normal embryos after testing?
- What is the chance of pregnancy after transfer of a normal embryo?
- What is the potential for needing multiple cycles to build a family?

Hypothetical Cycle Worksheet

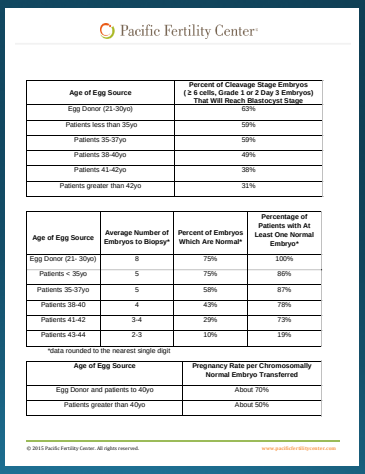


Pacific Fertility Center

HYPOTHETICAL CYCLE WORKSHEET

Timing in Cycle	Important Steps in Embryo Testing Process	Estimated #s
Baseline ultrasound. Begin injectable medications.	**Step 1** - Starting **Antral Follicle Count (AFC)** from your ultrasound (if more than one AFC on record, choose the most recent or average them; note that AFC approximates but does not necessarily equal the number of eggs retrieved)	
About 11-14 days from start of medications.	**Step 2 – Egg Retrieval** (Estimate **72%** of eggs retrieved to be mature)	
About 12-15 days from start of medications.	**Step 3 – Fertilization check**, assessment of number of normally fertilized eggs, or 2PNs (**64%** with conventional insemination as some eggs won't be mature, **80%** with ICSI as only mature eggs are injected)	
About 15-18 days from start of medications.	**Step 4** – Cleavage stage **(day 3) embryo assessment** (Estimate **69%** of 2PN will yield a growing day 3 embryo (grade 1 or 2 with at least 6 cells))	
About 17-20 days from start of medications.	**Step 5 – Blastocyst (day 5, 6, & 7) assessment and biopsy of embryos.** Samples will be sent to testing lab and embryos will be cryopreserved at Pacific Fertility Center. (see table on back for estimate of number of embryos which progress from cleavage to blastocyst stage (day 3 to day 5/6/7))	
About the time of expected menses. Approximately 10 working days from time that biopsied samples are sent.	**Step 6 – Chromosome Test Results*** (see table on back for estimate of the percentage of blastocysts that will be chromosomally normal and available for transfer)	
Typically after at least one rest menstrual cycle.	**Step 7 - Transfer of chromosomally normal embryo.** If no normal embryos, consideration of another IVF cycle.	1 embryo at a time, if available

Note: Results of your actual cycle may vary. Sometimes there are no embryos that grow to the blastocyst stage. Sometimes there are no chromosomally normal blastocysts after testing, and therefore no embryos to transfer.



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Age of Egg Source	Percent of Cleavage Stage Embryos (≥ 6 cells, Grade 1 or 2 Day 3 Embryos) That Will Reach Blastocyst Stage
Egg Donor (21-30yo)	63%
Patients less than 35yo	59%
Patients 35-37yo	59%
Patients 38-40yo	49%
Patients 41-42yo	38%
Patients greater than 42yo	31%

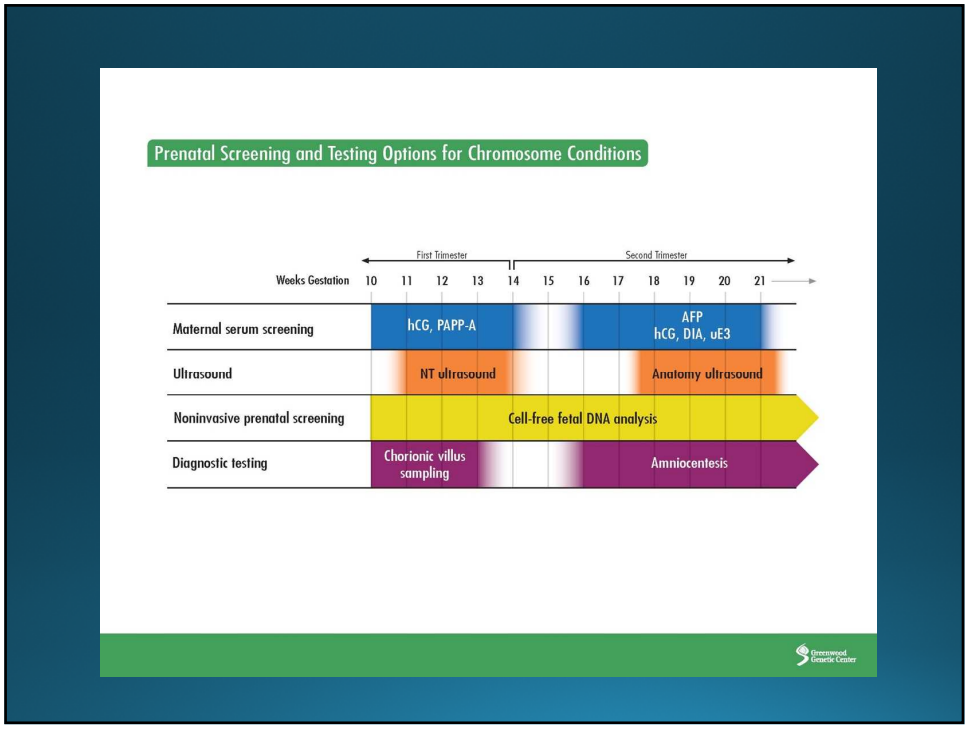
Age of Egg Source	Average Number of Embryos to Biopsy*	Percent of Embryos Which Are Normal*	Percentage of Patients with At Least One Normal Embryo*
Egg Donor (21- 30yo)	8	75%	100%
Patients < 35yo	5	75%	86%
Patients 35-37yo	5	58%	87%
Patients 38-40	4	43%	78%
Patients 41-42	3-4	29%	73%
Patients 43-44	2-3	10%	19%

*data rounded to the nearest single digit

Age of Egg Source	Pregnancy Rate per Chromosomally Normal Embryo Transferred
Egg Donor and patients to 40yo	About 70%
Patients greater than 40yo	About 50%

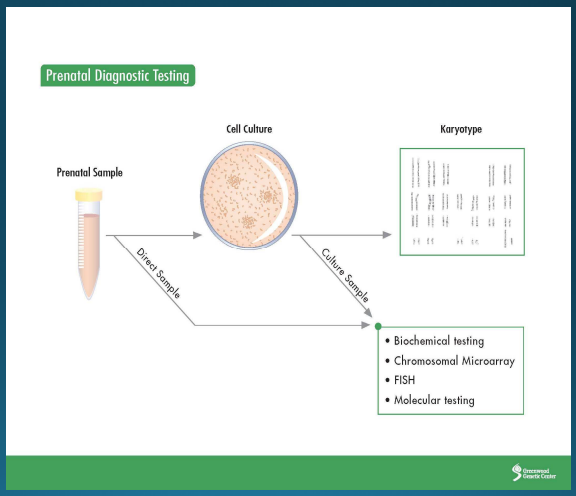
Factors in prenatal testing decision making

- Access to specific procedures (i.e. CVS, NIPT)
- Invasive nature and potential for miscarriage with diagnostic tests (CVS and amnio)
- Addressing risk as it arises in the pregnancy
- Limitations in detection rate for screening tests
- Availability of tests at a particular gestational age
- Impact of a possible misdiagnosis on pregnancy



Diagnostic prenatal tests

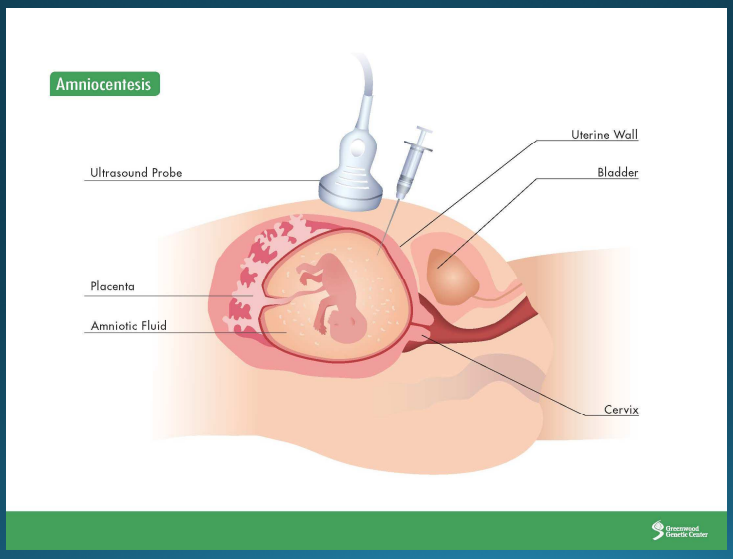
- Amniocentesis ("amnio")
- Chorionic Villus Sampling (CVS)



Amniocentesis

- More readily available of the two diagnostic tests
- Obtains sloughed fetal skin cells which are contained in amniotic fluid
- Risk for SAB less that 1% , likely 1/1600 (3)
- >99.9% detection rate for aneuploidy, and single gene disorders tested
- Typically offered between 16 and 20 weeks of gestation
- Fetal karyotype and/or microarray to confirm PGS
- Single gene DNA analysis to confirm PGD
- Also allows for quantification of alpha fetoprotein and acetylcholine esterase for screening fetal neural tube and abdominal wall defects.
- Considered the "gold standard" for fetal chromosome analysis

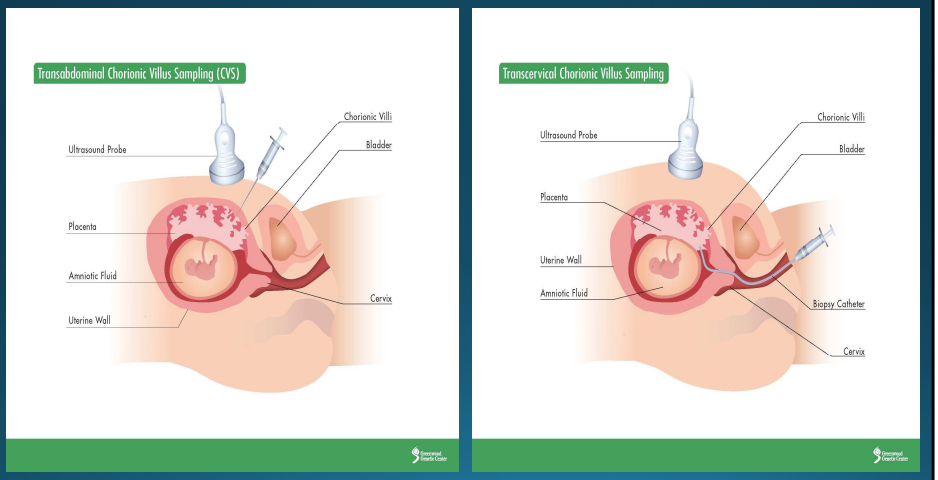
Amniocentesis procedure



Chorionic villus sampling (CVS)

- Less commonly available diagnostic test, not as many MDs trained to provide
- Obtains chorionic villi from placental (placental biopsy)
- May be higher and more provider dependent SAB risk compared to amniocentesis, but one study shows no significant difference in risk (4)
- >99.9% detection rate for aneuploidy, and single gene disorders tested
- 1-2% chance of mosaicism, typically confined to placenta (assessed by subsequent amniocentesis)
- Performed between 10 and end of 12 weeks of gestation
- Karyotype and/or microarray to confirm PGS
- Single gene DNA analysis to confirm PGD

CVS Procedure



Noninvasive prenatal screening options

- Maternal serum screening with or without ultrasound
- Ultrasound
  - Nuchal translucency (NT)
  - Fetal anatomy
- Cell free fetal DNA (aka non-invasive prenatal testing or screening (NIPT or NIPS))

Maternal serum screening

- Quantification of multiple maternal serum markers
  - Beta hCG (first and second trimester)
  - PAPP-A (first trimester)
  - Alpha fetoprotein (second trimester)
  - Unconjugated estriol (second trimester)
- Include nuchal translucency ultrasound to make the test more sensitive = **integrated screening**
- Marker levels along with other maternal variables used to calculate risk for:
  - Down syndrome, trisomy 18
  - Neural tube and abdominal wall defects
  - Smith Lemli Opitz syndrome and steroid sulfatase disorders
  - Informal risk assessment for late trimester complications
- Noninvasive, so no risk of SAB
- Limitations:
  - Lower detection rate for only two aneuploidies, higher false positive rates with AMA
  - No way to incorporate prior PGS into risk calculation algorithm

Estimated positive rates and detection rates with full integrated screening

Maternal Age	Screen Positive Rate for Down syndrome	Detection Rate for Down syndrome	Screen Positive Rate for trisomy 18	Detection Rate for trisomy 18
<35yo	3%	85%	0.12%	76%
>=35yo	14%	94%	1.41%	91%
All Ages	4.5%	90%	0.31%	81%

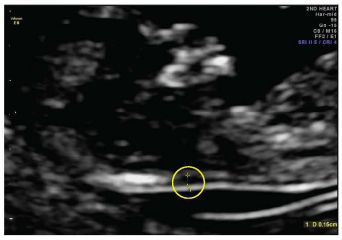
Full table available at State of CA Prenatal Screening website (5)

Fetal ultrasound

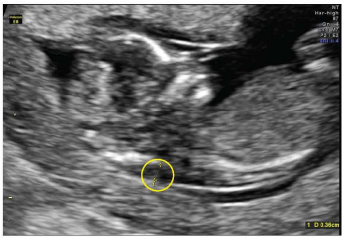
- Nuchal translucency
  - Performed in late first to early second trimester (10.5-14 wks GA)
  - Risk assessment for some aneuploidies (T21, T13/18)
  - Informal risk assessment for fetal structural anomalies and lymphedema
  - Typically combined with maternal serum screening or cfDNA
- Fetal anatomy survey
  - Typically performed in mid-second trimester (18-20 wks GA)
  - More detailed review of fetal anatomy
  - Certain ultrasound findings are associated with increased risk for aneuploidy

Nuchal Translucency (NT)

Normal



Increased

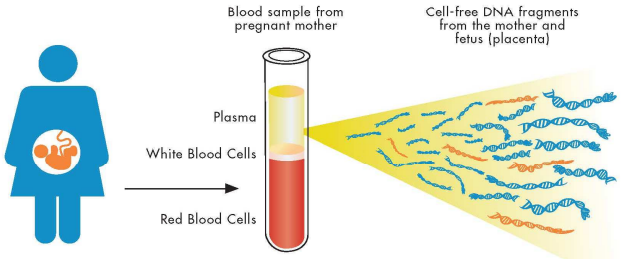


Greenwood Genetic Center

Cell Free Fetal DNA

- Newest non-invasive prenatal testing available as early as 9 weeks gestation
- Higher detection rate and lower false positive rate for Down syndrome compared to integrated screening
- Routinely screens for other common aneuploidies (T13, T18, 45,X, 47,XXX, 47,XXY and 47,XYY) but with lower accuracies
- Some labs are able to test for microdeletion syndromes and triploidy
- Single gene mutation analysis currently being investigated
- Some labs can't perform testing with egg donor or twin pregnancies

Cell-free Fetal DNA



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Accuracy of cell-free fetal DNA

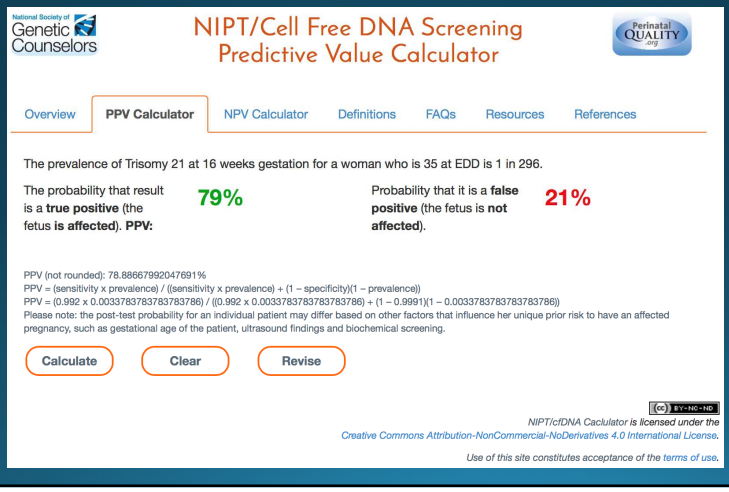
Aneuploidy	Detection Rate Among Various Labs*	False Positive Rate Among Various Labs*
Trisomy 21 (Down syndrome)	>99%	< or = 0.2%
Trisomy 18	96-99%	< or = 0.4%
Trisomy 13	80-99%	< or = 0.3%
Sex Chromosomes (45,X, 47,XXX, 47,XXY, 47,XYY)	67-99% (mostly in the 90 percentiles)	< or = 1.1%
Microdeletions and other aneuploidies (T16, T22)	60-99% - greater sensitivity for larger deletions, little data	<1%, little data

False Negative Rates Among Labs (T21, 13, 18 and 45,X combined) = 0.67-5.26%

*Data is a compilation of rates posted on websites amongst the four major labs that offer cfDNA: Natera (6), Sequenom(7), Illumina(8), and Ariosa(9). There is variability in part due to slightly different test platforms.

Positive Predictive Value Calculator

- www.perinatalquality.org
- Free calculator used by many prenatal genetic counselors when discussing a patients individual results



National Society of Genetic Counselors

NIPT/Cell Free DNA Screening
Predictive Value Calculator

Perinatal QUALITY .org

Overview | **PPV Calculator** | NPV Calculator | Definitions | FAQs | Resources | References

The prevalence of Trisomy 21 at 16 weeks gestation for a woman who is 35 at EDD is 1 in 296.

The probability that result is a **true positive** (the fetus **is affected**). **PPV:** **79%**

Probability that it is a **false positive** (the fetus is **not affected**). **21%**

PPV (not rounded): 78.886679920476691%
PPV = (sensitivity x prevalence) / ((sensitivity x prevalence) + (1 – specificity)(1 – prevalence))
PPV = (0.992 x 0.0033783783783783786) / ((0.992 x 0.0033783783783783786) + (1 – 0.9991)(1 – 0.0033783783783783786))
Please note: the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings and biochemical screening.

Calculate | Clear | Revise

Comparison of options

Test	Trimester	Risk of SAB	Detection for aneuploidy	Detection for single gene mutations	Detection of anatomic findings
CVS	1st	Yes	Yes, highly accurate	Yes, highly accurate	Not good, later ultrasound and maternal serum testing needed
Amnio	2nd	Yes	Yes, highly accurate	Yes, highly accurate	Yes, fetal anatomy and AF-AFP evaluated routinely
Maternal serum +NT (integrated)	1st and 2nd	No	Yes, detection rate variable (T21, T18)	SLOS screening only*	Yes, ONTD and AWD detected
cfDNA	Starting 1st through 2nd	No	Yes, detection rate variable (T21, T13, T18, SCAs)	Not currently, but likely in the future	No, fetal anatomy and MS AFP still needed
Anatomy ultrasound	2nd	No	No formal risk assessment but OR may be adjusted based on findings	No unless condition is associated with malformations	Yes, it's the point of the test

*Provided with California State Prenatal Screening Program

How can we help our patients understand the need for follow up prenatal testing after PGD/S?

- Consistent messaging throughout IVF clinic
- Appropriate pretest PGD/S counseling
- Reminder once a pregnancy is achieved, perhaps in the form of a FAQ sheet to be given to the patient as part of their "graduation" gift bag or paper work
- Education of the obstetrical care provider community
- Forward PGD/S lab report in transfer records to Ob/Gyn and/or give copy to patient

Conclusions

- There are some essential components of informed consent for PGD that all patients should understand prior to embryo testing.
- Genetic risk assessment is a useful and sometimes critical part of genetic counseling for PGD.
- Follow up prenatal testing is always recommended after PGD. There are various prenatal testing options with their associated benefits, limitations and risks.
- As PGD providers, we should all be committed to ensuring informed consent for PGD for our patients and supporting their knowledge of confirmatory prenatal testing options.

Thank you
for your attention.