Modifying Risk of Aneuploidy with a Positive Cell-Free Fetal DNA Result

A. Ashleigh Long, MD, PhD*, Alfred Z. Abuhamad, MD, Steven L. Warsof, MD

KEYWORDS

• Prenatal screening • NIPT • Noninvasive • Prenatal diagnosis • Prenatal risk • Aneuploidy

KEY POINTS

- Despite superior sensitivities and positive predictive values of noninvasive prenatal testing (NIPT) screening beyond traditional screening, a positive cell-free fetal DNA (cfDNA) result should not be considered a diagnostic test and should be verified by karyotyping through an invasive testing method, such as chorionic villous sampling, or amniocentesis.
- NIPT screening should be completed in conjunction with an early ultrasound evaluation, which would incorporate the superior accuracy of cfDNA molecular analyses with the early morphologic evaluation of the fetus.
- The use an early morphology ultrasound examination in conjunction with cfDNA screening in a general obstetrics population has several advantages.
- These advantages include highly accurate dating of gestational age, early detection of multiple gestations, determination of chorionicity and the early detection of twin-twin transfusion syndrome, early detection fetal abnormalities, and early detection of congenital heart disease.

BACKGROUND

Screening and diagnostic testing for chromosomal aneuploidy have been available since the 1970s, when the karyotyping of fetal cells from amniotic fluid obtained through amniocentesis was first performed.[1] Invasive diagnostic procedures and karyotyping could not feasibly be performed on all pregnancies; therefore, screening strategies were developed to determine which pregnancies should be offered diagnostic testing. In general, the most effective screening programs were those with sensitivities

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Department of Obstetrics and Gynecology, Eastern Virginia Medical School, 825 Fairfax Avenue, Suite 500, Hofheimer Hall, Norfolk, VA 23507, USA
* Corresponding author.
E-mail address: longaa@evms.edu

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as high as possible approaching 100% with false positive or screen positive rates as low as possible.

Initial screening strategies in the 1970s and early 1980s relied on maternal age and family history of aneuploidy. If the patient was aged 35 (Down syndrome [DS] risk of 1:270) or greater at the time of delivery, or had a first-degree family history of aneuploidy, women were offered invasive diagnostic testing either by amniocentesis in the second trimester or with chorionic villous sampling (CVS) using a transcervical or transabdominal approach in the late first trimester. Although this screening was accepted by a large segment of the population, it had poor sensitivity (25%–30%) for aneuploidy detection, and a high selection or false positive rate (15%–20%), resulting in a large number of invasive diagnostic procedures with few aneuploidies detected. This strategy missed 70% to 75% of aneuploidies as most aneuploidies are born to women less than the age of 35. In some countries, maternal age of 38 (1:150 risk of DS) or 40 (1:100 risk of DS) were used as alternate screening criteria based on financial and medical resources to provide genetic screening services in these countries, which led to an even lower sensitivity, but with fewer invasive procedures.

Subsequent development of additional screening methods in the late 1980s focused on the second trimester of gestation with screening strategies that measured serum levels of maternal serum analytes, Maternal Serum Alpha Fetal Protein (MSAFP), Beta Human Chorionic Gonadotrophin (BHCG), serum levels of unconjugated estriol (uE3), and Inhibin. In the late 1990s, additional late first-trimester screening was developed using the combination of ultrasound nuchal translucency measurements and with BHCG and Plasma-Associated Pregnancy Protein A (PAPP-A) serum analytes; this increased the sensitivity of aneuploidy detection to 80% to 85% while decreasing the false positive rate to 5%. Combinations of first- and second-trimester strategies were referred to as integrated, sequential, or contingency screening and increased the sensitivity for aneuploidy to 95% while still maintaining the 5% false positive rate.

Although these developments enhanced sensitivity and detection rates, the 5% false positive rate implied that the positive predictive value (PPV), which varies with the prevalence of the disease in the screened population, remained quite low, especially in the younger pregnant population with low prevalence of aneuploidy. The PPV ranged from 1% in maternal age 15 to 19 with prevalence of aneuploidy of 1:1667 to 20% in the maternal age 40 to 44 when the prevalence of aneuploidy is 1:67 (**Table 1**).

Table 1
Positive predictive value of trisomy 21 screening tests vary by maternal age

Maternal Age	Incidence of DS	No. of Live Births with DS	NIPT	FTS	MSAFP4
—	—	Sensitivity	99	85	75
—	—	False +	0.1%	5%	5%
15–19	1:1667	198	37%	1.0%	0.9%
20–24	1:1448	621	40	1.1	1.0
25–29	1:1118	1008	47	1.5	1.3
30–34	1:742	1328	57	2.2	1.9
35–39	1:239	1937	80.6	6.6	5.9
40–44	1:67	1611	93.7	20	18.4
>45	1:19	366	98.1	48	45

The incidence of trisomy 21 varies dramatically by age, as does the PPV of prenatal screening tests, which include NIPT, first-trimester screening (FTS), and maternal serum markers, such as MSAFP.