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The Impact of New Commercial Tests Evaluating Cell-free Fetal DNA in Maternal Circulation for Aneuploidy Detection in High-risk Patients

Camille Campion
Bates College

Meredith Rochon MD
Lehigh Valley Health Network, Meredith_L.Rochon@lvhn.org

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The impact of new commercial tests evaluating cell-free fetal DNA in maternal circulation for aneuploidy detection in high-risk patients

Campion, C; Rochon, M.

Lehigh Valley Health Network, Allentown, Pennsylvania

Background

- Fetal aneuploidy is an abnormal number of chromosomes in a fetus's DNA caused by missing or extra chromosomes that originate during cell division.
- An abnormal number of chromosomes can result in genetic disorders and birth defects.
- Three most common types of aneuploidy
  - Trisomy 21 (Down syndrome)
  - Trisomy 18 (Edwards syndrome
  - Trisomy 13 (Patau syndrome)
- Screening for fetal aneuploidy is important in both low-risk and high-risk pregnancy patients.
- Invasive tests, amniocentesis and chronic villus sampling (CVS), provide the most accurate information, but are associated with a small risk of miscarriage.
- Non-invasive tests, performed by obtaining maternal blood, are not associated with a risk of miscarriage but they do not have high accuracy with detection rates of 70-92% for aneuploidy (1).
- Cell-free fetal DNA (cffDNA), introduced in the fall of 2011, is a new form of non-invasive aneuploidy tests for the diagnosis of fetal trisomy 13, 18, and 21
  - Sensitivities and specificities for the three different aneuploidies approach 100% (2).
- **The purpose of this study is to assess how the introduction of cffDNA tests on a population of high-risk patients from Maternal Fetal Medicine of LVHN has affected the use of invasive procedures in the practice over a period of time.**

Methods

- Retrospective cohort study
- Inclusion criteria:
  - Women determined to be at high-risk for aneuploidy seen in Maternal Fetal Medicine at LVHN from 1/01/2012 to 12/31/13, who underwent cffDNA testing
- Indicators of "high-risk":
  - Advanced maternal age (AMA-maternal age ≥ 35)
  - Abnormal maternal serum screen
  - Abnormal ultrasound findings
  - Family/personal history of aneuploidy
- Exclusion criteria:
  - Women at low-risk for fetal aneuploidy
- Tests performed during this study period:
  - MaterniT21 Plus (*Sequenom CMM*)
  - Verifi Prenatal Test (*Verinata*)
  - Harmony Prenatal Test (*Integrated Genetics*)
- Results were reported as:
  - Mat21: "positive", "negative", or "non-reportable"
    - Non-reportable results were due to insufficient fetal DNA from maternal serum and women were offered a redraw on an invasive test
  - Verifi: "aneuploidy detected", "aneuploidy not detected", or "unclassifiable"
    - Unclassifiable results are those found to be in the "gray zone" or overlap between what is considered positive and negative for a specific aneuploidy
      - Women with this result were not offered a redraw per lab protocol but were offered invasive testing
  - Harmony: "high-risk" or "low-risk"
- Neonatal records and maternal postpartum visit records were reviewed whenever possible to confirm neonatal outcome and identify false positive and/or false negative results
- Descriptive statistics were generated using Excel 2010
- Utilization of cffDNA as compared to invasive testing over time was determined

Results

Figure 1: Primary indication for cffDNA screen

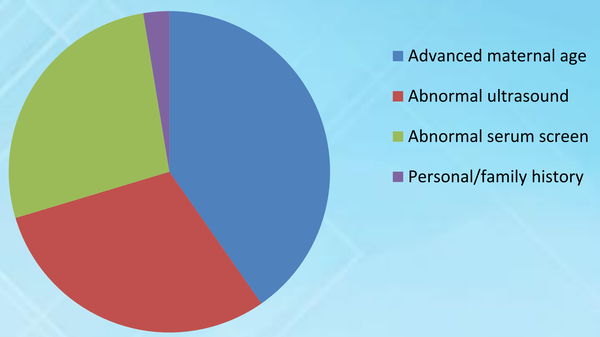


Table 1. Results of cell-free fetal DNA testing

Negative	922/956 (96.4%)
Positive	28/956 (2.9%)
Non-reportable	5/956 (0.5%)
Unclassifiable	1/956 (0.1%)

Table 2. Pregnancy continuation after positive results

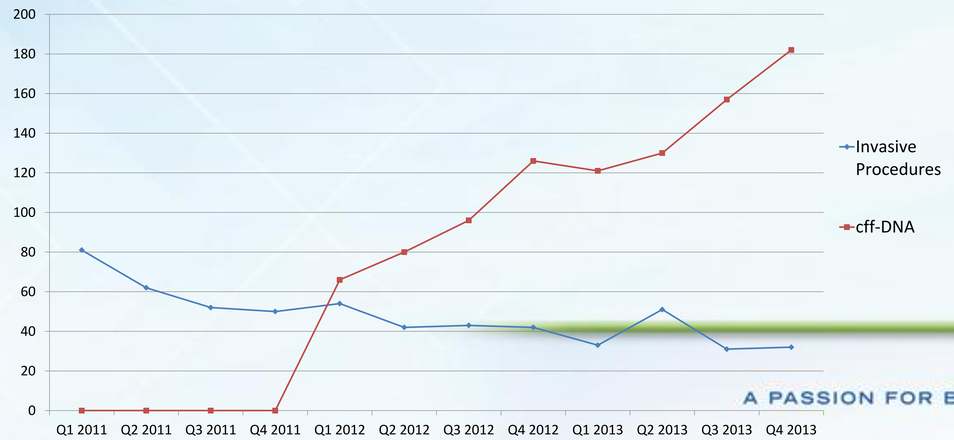
Continuation of pregnancy	19/28 (67.9%)
Live birth	16/19
Miscarriage	3/19
Termination	9/29 (32.1%)

Table 3. Test performance for detection of Trisomy 21*

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Trisomy 21	94.7%	100%	100%	99.9%

*For the results that were confirmed by karyotype

Figure 2. Cell-free fetal DNA test utilization over the first two years offered as compared to the utilization of invasive procedures



Results

- 958 patients underwent cell-free fetal DNA testing during the study period. 2 cancelled the test prior to getting results for a total cohort of 956 patients
- Advanced maternal age was the most common indication for testing (Figure 1)
- 13 patients had non-reportable results on initial testing. Of the 12 that were retested, 4 results remained unreportable and the rest returned negative.
- There were 28 (2.9%) positive and 1 (0.1%) unclassifiable results (Table 1). The majority of the positive results were trisomy 21.
- Only 9 patients opted to confirm abnormal results with invasive testing. All women with confirmed abnormal results on invasive testing terminated the pregnancy.
- Of the women with positive results, 68% continued the pregnancy (Table 2).
- Test performance was high (Table 3).
- Cell-free fetal DNA test utilization increased significantly over time (Figure 2) and was associated with a concomitant decrease in the number of invasive tests being performed.

Conclusion

- Cell-free fetal DNA (cffDNA) is a new prenatal aneuploidy screening test being used with increasing frequency in high risk obstetrical patients
- As utilization of cffDNA is increasing, performance of invasive (diagnostic) procedures is decreasing
- Although detection rates are much better than older aneuploidy screening tests, cffDNA should be considered a screen, not a diagnostic test, as it does have rare false positive and false negative results. It is therefore important to confirm positive cffDNA results with an invasive test.
- Future studies should look at test performance in low-risk populations.

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