IMPLEMENTATION OF NON-INVASIVE ANEUPLOIDY SCREENING

Mindy Simonson, ScM, CGC
Genetic Counselor, UAMS Arkansas Reproductive Genetics Program
Non-Invasive Prenatal Screening for Aneuploidy

- NIPD – NIPT – NIPS – ccffDNA.
- Quantitative assay for differences in amount of cell-free DNA in maternal serum.
- Detects trisomies 21, 18, and 13, monosomy X, and other sex chromosome anomalies.
- Available after 10 weeks.
- $800 - $2100 list price, many insurance companies now cover this testing, some companies have OOP maximums.
Performance

- 7 Published Studies in high risk populations.
- ~2% have insufficient fetal DNA for testing, most succeed on re-draw.
- Down syndrome:
  - Detection rate of 99.3% (CI 98.2-99.8%)
  - FPR of 0.16% (CI 0.08-0.31%) (not including unclassified results)
- Trisomy 18:
  - Detection rate of 97.4% (CI 93.7-99.0%)
  - FPR of 0.15% (CI 0.07-0.31%)
- Trisomy 13:
  - Detection rate of 78.9% (CI 65.9-91.9%)
  - FPR of 0.41% (CI 0.22-0.61%)
Performance

- Turner syndrome:
  - Detection rate of 83%
  - FPR 0.2%

- Other SCA:
  - 75-85% detection, one FP
  - Limited numbers

- Gender:
  - Correctly assigned in 99.4% of cases
Multiples

- Two studies.
- All twins were correctly classified, but between two studies <40 twin pairs.
- Does not distinguish between concordant and discordant twins, and cannot identify which is affected twin.
- In cases with a vanishing twin, treat an abnormal result with caution.
UAMS Experience

- Began offering testing in May 2012.
- As of August 2013, we have sent 204 tests.
- 1.6% (3/204) had insufficient fetal DNA for testing.
- 24/204 have been abnormal (11.8%):
  - Down syndrome – 8
  - Trisomy 18 – 8
  - Trisomy 13 – 1
  - Monosomy X – 3
  - Abnormal but ambiguous – 4
Ambiguous results:

- Oligo/+AFP – equivocal T18 risk, PTD, but normal chromosomes.
- MCA – “partial chromosome 18 anomaly”, IUFD at 29 weeks, no growth for karyotype.
- Lagging FL, MCA, low chromosome 18 material, delivered, 46, XY, with a duplication of 17q and a deletion of 18q (!)
- +DS, nml US, initial result 46 XY (phenotypically female), on repeat testing, XX, but weak positive for T21.
No known false negatives.

- Two cases of triploidy.
- One case with a ring chromosome derived from chromosome 13 with partial deletion of 13.
UAMS Experience

- **Turn around time:** average 8.37 days, varies from 5 to 17 days.
  - Varies by lab, and TAT has been decreasing.
- **We use MaterniT21 Plus, Harmony, and Verifi.**
  - Varies based on indication and insurance coverage.
Current Recommendations

- ACOG Committee Opinion – December 2012:
  - Recommends offering NIPT to women at increased risk:
    - Maternal age of 35 years or greater at delivery.
    - Ultrasound findings that increase risk of aneuploidy.
    - History of a prior pregnancy with aneuploidy.
    - Prior positive test for aneuploidy (Quad, first trimester, etc.).
    - Parental balanced Robertsonian translocation with increased risk for T21 or T13.
  - Do not yet recommend for low risk women and multiples.
  - Recommends invasive testing for pregnancies with anomalies.
Current Recommendations

- NSGC (June 2012) – “supports as an option for patients whose pregnancies are considered to be at an increased risk for certain chromosome abnormalities.”

- ACMG (Feb. 2013) – focuses on limitations and pre/post-test counseling. Encourages providers to consider PPV and NPV.
Positive Predictive Value – High Risk

1000 patients

10 pregnancies with Down syndrome

990 pregnancies without Down syndrome

99.3% Detection
10 screen positive

0.16% FPR
1-2 screen positive

Therefore:
Positive Predictive Value = 10/11 = 90.9%
Positive Predictive Value – Average Risk

1000 patients

1 pregnancy with Down syndrome

999 pregnancies without Down syndrome

99.3% Detection

1 screen positive

0.16% FPR

1-2 screen positive

Therefore:
Positive Predictive Value = 1/2 = 50%
Pre-Test Counseling

- ACMG recommends:
  1. Explanation of purpose of NIPT/S.
  2. Advantages compared to maternal serum analytes, including higher detection, high negative predictive value, lower false positive rate, and risk assessment less dependent on gestational age.
  3. Considerations for follow-up invasive testing if positive.
  4. Limitations of NIPT/S. (only screens for trisomies 13, 18, and 21, cannot distinguish trisomy from an unbalanced translocation, can have uninformative results, turn around time, does not screen for ONTDs, does not replace ultrasound, limited information on multiples, does not predict pregnancy complications.)

- Other thoughts?
  - Cost/insurance coverage?
Post-Test Counseling

- **ACMG recommends:**
  1. Possibility of false positive (due to vanishing twin, CPM).
  2. NIPT/S is not diagnostic, risks and benefits of amnio and CVS should be reviewed.
  3. If prenatal diagnosis is declined, patient should be counseled about post-natal confirmation.
  4. Accurate, up-to-date information about the condition should be provided. (brightertomorrows.org, etc.)

- **Other thoughts?**
  - Prenatal/neonatal management?
Questions? Comments? Concerns?

MESimonson@uams.edu
501-296-1745 x1406

References available.