Non-Invasive Prenatal Testing

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Prenatal testing

- **Non-invasive –**
  - Abdominal ultrasound (US)
  - Nuchal translucency US or nuchal fold scan
  - Triple or quadruple screening – hCG, AFP, estriol, Hormone inhibin A
  - Cell-free fetal DNA testing
- **Invasive –**
  - Chorionic villus sampling
  - Amniocentesis
  - Cordocentesis (PUBS)

Intended Uses

- High-risk pregnancy – diabetes, cancer, high blood pressure, > 35 yo, past problems in past pregnancy, infections, etc
- Screening
- Diagnosis

Non-Invasive Prenatal Testing (NIPT)

- **Maternal peripheral blood sample**
- **Detects circulating, cell-free fetal DNA as early as 10 wks**
- Screening for fetal aneuploidies with MPS (chr 21, 18, 13 trisomies)
  - Sequenom – MaterniT21
  - Illumina – Verinata verify™
  - Roche (Ariosa) – Harmony Prenatal Test ™
- **SNP-based tests – trisomies and fetal sex**
  - Natera – Panorama™

Limitations of testing

- Initially validated for use in high-risk pregnancies
- As early as 10 weeks gestation
- Intended as screening tests
- Abnormal findings to be confirmed by diagnostic testing (amniocentesis or CVS) *prior* to decisions about whether to terminate a pregnancy
- Not appropriate for many known genetic abnormalities, ie normal NIPT does not rule out other genetic disorders

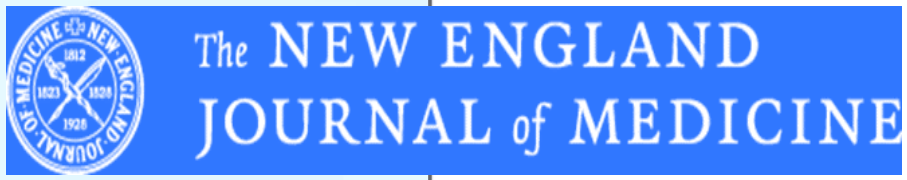
Concerns of Stakeholders

- Patients
- Physicians
- Laboratories
- Regulators
- Ethics, legal , & social issues

Noninvasive Examination of Trisomy (NEXT) study*

- Blinded prospective study compared
  - Cell-free fetal DNA (cfDNA) testing - Ariosa's Harmony test
  - First trimester biochemical and nuchal translucency
- 15,841 pregnant women (at least 18 yo) at average risk for fetal abnormalities
- 35 centers in 6 countries
- The positive predictive values of cfDNA testing and standard screening for trisomy 21 were 80.9% and 3.4%, respectively.
- cfDNA testing had higher sensitivity and specificity.

Enrollment and Outcomes.



Norton ME et al. N Engl J Med 2015;372:1589-1597

Possible solutions

- **Education of stakeholders – genetic consultation pre-test and post-test**
- **Additional test validation requirements**
- **Clearer test labeling –**
  - indications
  - limitations
  - interpretations
  - follow-up confirmatory testing

Questions for CLIAC

- **What should labs performing NIPT disclose**
  - Assay validation for different patient populations? (high-prevalence of genetic disorders vs general population)
  - Performance specifications for aneuploidy detection?
  - Regarding risk interpretation in result reporting?
  - About confirmatory diagnostic testing?
- **How can laboratories help physicians and patients be better informed about the limitations and appropriate use of NIPT?**
- **Is there a role for FDA/CMS/CDC in providing that information?**