To examine the performance of noninvasive prenatal testing for sex chromosome aneuploidy (SCA) and fetal sex using genome-wide massively parallel sequencing, we performed SCA analysis on fetal sex. Limited data is published on its clinical validity. This study examines SCA test performance and highlights clinical management dilemmas for which no medical guidelines currently exist.

**Objective:** Noninvasive prenatal testing (NIPT) has quickly evolved to include sex chromosome aneuploidy (SCA) and identification of fetal sex. Limited data is published on its clinical validity. This study examines SCA test performance and highlights clinical management dilemmas for which no medical guidelines currently exist.

**Study Design:** Clinical laboratory results were reviewed for samples with SCA analysis, including follow-up information when available.

**Results:** SCA analysis is optional at the time of testing for autosomal aneuploidy. During the study period, 18,161 samples were tested for SCA. In 17,957 (98.88%) of cases, no SCAs were detected; XX or XY was reported. SCAs were detected in 204 cases (1.12%) (see Table). A false positive rate of 0.26% is estimated based on available clinical follow-up information. One fetus called XY by NIPT test result demonstrated a mother in false-pregnant kidney transplant from a male donor. In an ongoing pregnancy a fetus called XY by NIPT has ambiguous genitalia and multiple anomalies.

**Conclusion:** Early trends in clinical laboratory experience with NIPT for SCA analysis show a low putative false positive rate. When the fetal sex is reported as XX or XY, the maternal SCA mosaicism, twin demise, fetal under- or over-masculinization, or a maternal solid organ transplant.

**Results:**

- 18,161 cases were tested for SCAs during the study period.
  - Results were detected in 17,957 (98.88%) (see Table 1).
  - In these cases, XX or XY was reported.
  - Karyotype was normal in 17,957 (98.88%), which is in line with 1,035 as reported in 2012 U.S. birth statistics.
- SCAs were detected in 204 cases (1.12%) (Figure 2, Table). A false positive rate of 0.26% is estimated based on available clinical follow-up information.

**Discussion**

**Possible Biological and Technical Explanations:**

- **Fetal sex by NIPT is XX but fetal sex is female in female carriers of SCA:**
  - Co-se develeopment.
- **Fetal sex by NIPT is XY but fetal sex is female in female carriers of SCA:**
  - Co-se develeopment.
  - Misfemale.
  - Confused karyotype.
- **Fetal sex by NIPT is XX but fetal sex is male in male carriers of SCA:**
  - Co-se develeopment.
- **Fetal sex by NIPT is XY but fetal sex is male in male carriers of SCA:**
  - Co-se develeopment.
  - Misfemale.
  - Confused karyotype.
- **SCA Detected by NIPT but fetal sex is female in female carriers of SCA:**
  - Ultrasound outcome.
  - Anomalies.
  - Now a male sex-reassign.
  - Contact NIPT laboratory to discuss sex results.
  - Ultrasound outcome.
  - Now a female sex-reassign.
  - Contact NIPT laboratory to discuss sex results.
  - Ultrasound outcome.
  - Now a male sex-reassign.
  - Contact NIPT laboratory to discuss sex results.
  - Ultrasound outcome.
  - Now a female sex-reassign.
  - Contact NIPT laboratory to discuss sex results.
  - Ultrasound outcome.
  - Now a male sex-reassign.

**Clinical Management Considerations:**

- **Reassure the parents:**
  - To rule out findings suggestive of over-masculinization conditions.
  - Contact NIPT laboratory to discuss sex results and utility of repeating NIPT.
  - CV/Onychodactyly.

**Conclusions**

- Early trends suggest SCA and fetal sex testing perform well, or better, than the expected parameters established in validation studies.
  - With high accuracy, cases of fetal sex discordance are expected to occur for a variety of biological reasons, such as:
    - Maternal SCA (mono or full).
    - Maternal X chromosome variant.
    - Co-se devise.
    - Fetal under- or over-masculinization due to single gene disorders.
    - Maternal organ or bone marrow transplant from a male donor.
  - Clinical management should consider all possible reasons for discordance and manage such cases accordingly.

**References**