Estimation of fetal fraction-based risk and redraw success rate in cases that are not callable by NIPT

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Objective
Recent reports have indicated that a low fetal fraction (FF) of cell-free DNA in maternal plasma may be associated with increased risk for fetal trisomy 13 (T13), trisomy 18 (T18), or digynic triploidy (3n). By modeling the effect of these abnormalities on fetal fraction, a FF-based risk score can be computed for cases that do not produce an NIPT result due to low FF.

Methods
FF distributions for chromosomally normal cases were modeled based on approximately 165,000 presumed normal pregnancies referred for NIPT. Distributions for abnormal cases were estimated from 496 samples (T18, 343; T13, 144; 3n, 9). FF-based data likelihoods were computed by comparing the observed FF against the various model distributions. The FF-based risk score, which provides an estimated risk of abnormality for the individual case when a call cannot be made using the SNP-based Panorama NIPT method, was defined as the estimated probability of a T18, T13, or 3n abnormality. It was computed from the observed FF data likelihoods and the age-based prior risk.

One ratio was estimated for T13 and T18 affected pregnancies and another for 3n, using a maximum-likelihood approach. Compared with chromosomally normal pregnancies, T13 and T18 reduced the FF by a ratio of 0.79 and 3n reduced the FF by a ratio of 0.22. The FF for trisomy cases in the modelling data fit a log-normal distribution with p=0.13 (Kolmogorov-Smirnov test). In the pilot study of very low fetal fraction, karyotype information was successfully collected in 58/113 (51%) cases. The positive follow-up results included one T13, two T18, and four 3n (total of 7/58); for a combined PPV of 12.1% (95% CI 5.0–23.3). Assuming that all cases without follow-up are normal (total of 7/113), the conservative PPV would be 6.2% (95% CI 2.5–12.4). Analysis of samples undergoing redraw showed that redraw success rate depended on a combination of FF of the initial draw and maternal weight. For example, for patients with initial FF between 3 and 4%, the success rate after redraw was approximately 70% for maternal weight <130 pounds and <50% for maternal weight >225 pounds. Note that redraw success rate depends on the absolute fetal fraction but that FF-based risk depends on the relative FF adjusted for both maternal weight and gestational age.

Conclusion
This method provides a patient-specific risk score in cases where NIPT fails due to low FF. In this pilot study of women identified as having high FF-based risk score, the PPV of a high-risk call was 12.1%. Using a combination of FF of the initial draw and maternal weight, we were also able to estimate the probability of success for a redraw. This information, in combination with targeted sonography, should be useful for counseling patients and determining a care plan.