

# A novel Bayesian hierarchical model for analytically validating the detection of common and rare autosomal aneuploidies from noninvasive prenatal screening of 44,420 samples

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## BACKGROUND

- Rare autosomal aneuploidies (RAAs) are individually rare but collectively common and associated with poor pregnancy outcomes.
- Recent advances in whole-genome sequencing-based noninvasive prenatal screening (WGS-based NIPS) have allowed it to screen for rare autosomal aneuploidies (RAAs).
- We present the results of a statistical modeling framework to assess the analytical validity, at clinically relevant fetal-fraction levels, of a WGS-based NIPS that can detect aneuploidy on all autosomes.

Figure 1. Simulations recapitulate observed data (chromosome 7)

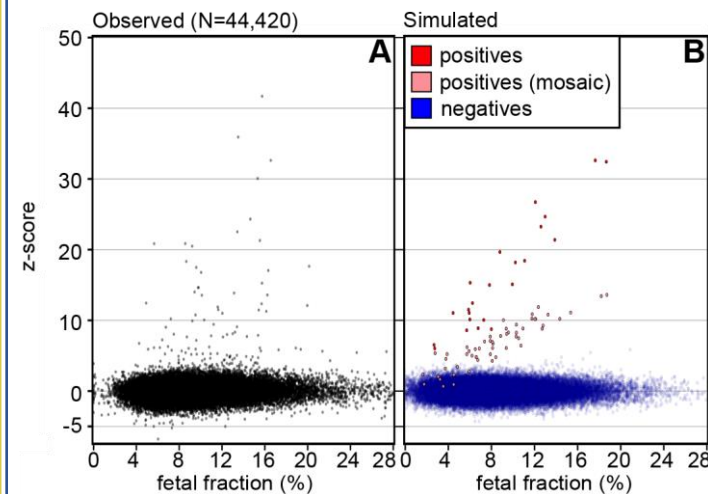
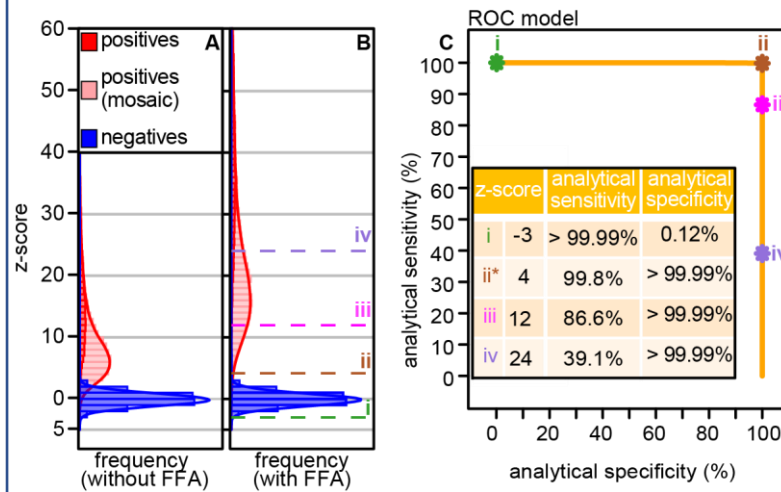


Figure 2. FFA boosts sensitivity for RAA (chromosome 7)



## METHODS

- We utilized Markov Chain Monte Carlo (MCMC) to estimate the parameters of a Bayesian hierarchical model that models the relationship between fetal fraction, read depth, and aneuploid signal (i.e., z-score) using 44,420 WGS-based NIPS patient samples.
- The presence of confined placental mosaicism was also incorporated into the model to better characterize performance across RAAs.
- Fetal fraction amplification (FFA), which enriches the proportion of fetal-derived reads for NIPS, was also modeled to assess its effect on performance.
- A receiver-operator characteristic (ROC) model was constructed to optimize test performance.

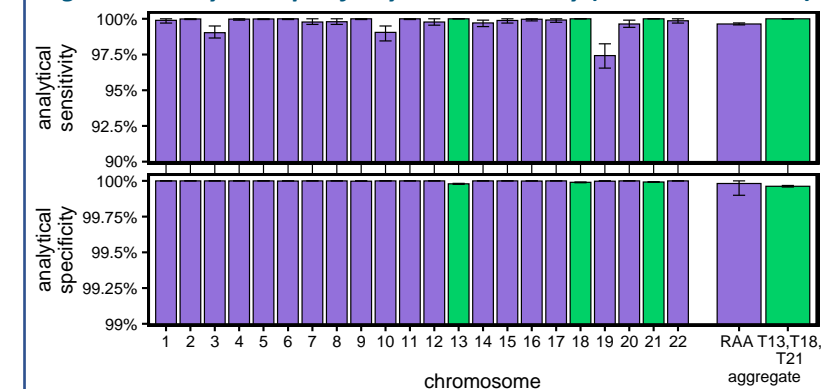
## RESULTS

- MCMC simulation reproduced the observed relationship between fetal fraction and z-score for chromosome 7 (Figure 1).
- FFA boosted sensitivity for RAAs by increasing the z-scores of mosaic samples (Figure 2).
- For RAAs with FFA, aggregate analytical sensitivity was 99.64% and joint analytical specificity was 99.98%. For common aneuploidies (T13, T18, T21), aggregate analytical sensitivity was >99.99% and joint analytical specificity was 99.96% (Figure 3).

## DISCUSSION

- Utilizing a Bayesian hierarchical model and MCMC simulation, we were able to demonstrate both high analytical sensitivity and specificity of a commercially available WGS-based NIPS for detecting common and rare fetal autosomal aneuploidies across a spectrum of fetal fractions, while also accounting for the effects of placental mosaicism.

Figure 3. Analytical specificity and sensitivity (all chromosomes)



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