# How positive is your prediction? Computing confidence intervals on positive predictive value for non-invasive prenatal screening

Imran S. Haque, PhD; Carrie Haverty, MS LCGC; James D. Goldberg, MD; Eric A. Evans, PhD

*South San Francisco, California*

## Introduction

While non-invasive prenatal screening (NIPS) for fetal aneuploidy has high sensitivity and specificity, prevalence varies significantly by maternal and gestational age. Variable prevalence affects the probability that a positive test indicates an affected fetus (positive predictive value, PPV). While ACMG[1] directs laboratories to report PPV individualized to the particular patient, previous work has not addressed how uncertain PPV calculations are or to what precision PPV can be estimated.

## Methods

Positive predictive value is a function of condition prevalence, test sensitivity, and test specificity. Uncertainty in any of these parameters will affect the size of the confidence interval for PPV:

$$\mathrm{PPV} = \frac{TP}{TP + FP} = \frac{\mathrm{SENS} \times \mathrm{PREV}}{\mathrm{SENS} \times \mathrm{PREV} + ((1 - \mathrm{SPEC}) \times (1 - \mathrm{PREV}))}$$

For all three, uncertainty arises from the size of the dataset used to estimate the parameter (e.g., the number of tests used to estimate sensitivity and specificity, or the size and length of population surveillance/data collection for condition prevalence), with larger datasets providing more certainty about the value of a parameter.

Note that *uncertainty* and *accuracy* are two different concepts: it is possible to have a very accurate test and be uncertain about the precise value of its accuracy, or conversely to have an inaccurate test and be confident in the estimate of the value of its accuracy (Fig 1).

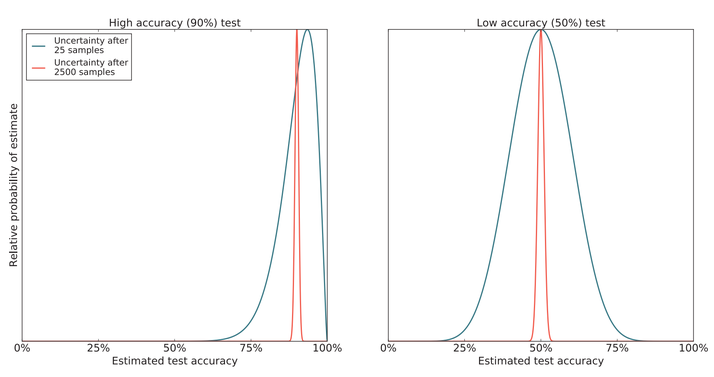


Figure 1

**Performing a smaller study (blue) makes us less confident in the exact value of the accuracy of a test than if we had performed a larger study (red), regardless of whether the test is accurate (left) or inaccurate (right)**

## Sampling uncertain values

Test sensitivity and specificity are reported as point estimates with 95% confidence intervals[2] and can be modeled by fitting a beta distribution to these three parameters.

Population studies of common aneuploidies (trisomies 13, 18, and 21)[3,4] typically analyze population health records and report the number of total pregnancies and the number of trisomy-positive pregnancies at each maternal age. These data are then fit by regression[4] to generate a modeled curve estimating population prevalence by maternal age.

These counts can be used as parameters to a beta distribution (Fig 1), from which samples may be repeatedly drawn and regression repeated in order to estimate uncertainty in the final estimate of prevalence (Fig 2):

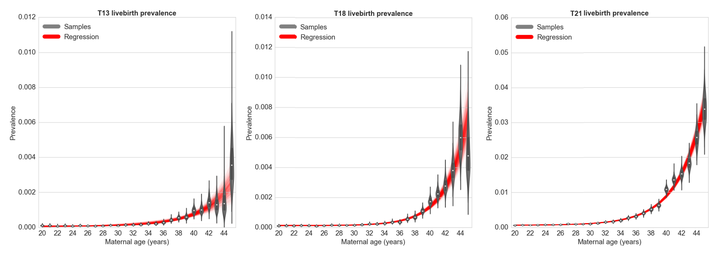


Figure 2 **Population data on birth prevalence is used to parametrize a beta distribution at each maternal age (gray). Samples can be repeatedly drawn from these distributions; regression on each sample produces a family of estimates for the modeled prevalence function (red)**

Prevalence by gestational age is typically modeled as a probability of fetal demise at each gestational age and may be modeled using the beta-regression method above[4] or by bootstrap resampling of the Kaplan-Meier fetal demise curve[5] depending on the available data (Fig 3).

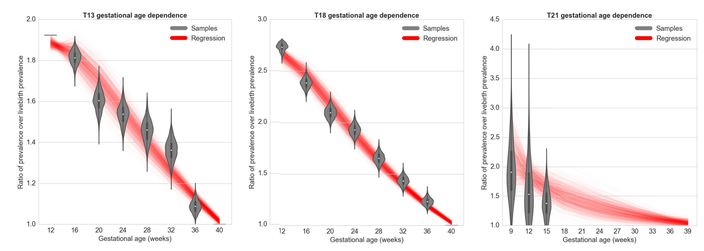


Figure 3 **Samples of gestational prevalence for T13, T18, and T21**

## Study results

Even incorporating uncertainty, PPV CIs are well-separated between maternal ages, suggesting that patient-specific PPVs are statistically significant and add value to counseling (Fig 4).

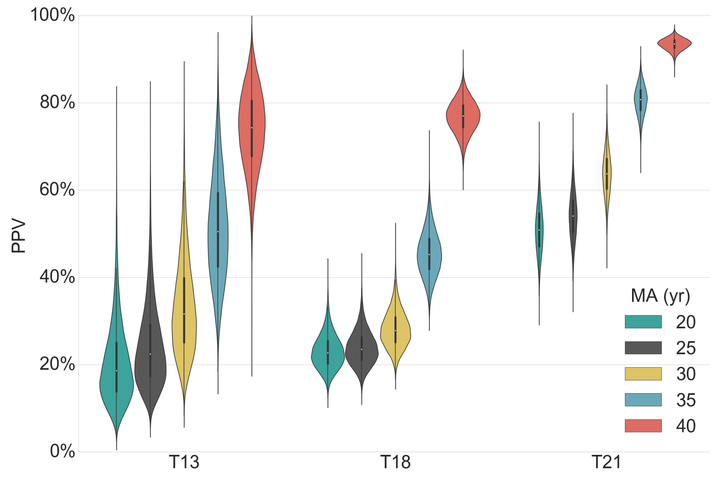


Figure 4 **Distribution of positive predictive values for T13, T18, and T21 at a fixed gestational age of 16 weeks, at maternal ages of 20, 25, 30, 35, and 40 years**

Using analytical parameters from a small, single-source study[7] produces PPVs that are inconsistent with those determined from meta-analyses, showing the importance of using large studies to evaluate performance (Fig 5).

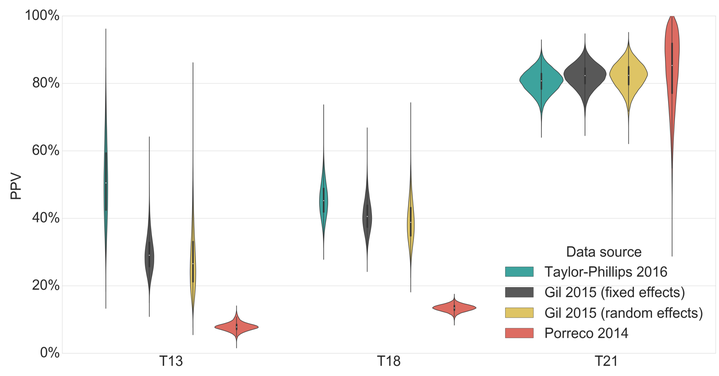


Figure 5

**PPV distribution for T13/T18/T21 at a fixed gestational age of 16 weeks, and fixed maternal age of 35 years, with analytical parameters drawn from different studies**

By sampling over subsets of parameters, it is possible to determine that most of the uncertainty in PPV is controlled by uncertainty in NIPS specificity, followed by prevalence (Fig 6). Sensitivity is well-determined and contributes little to PPV uncertainty.

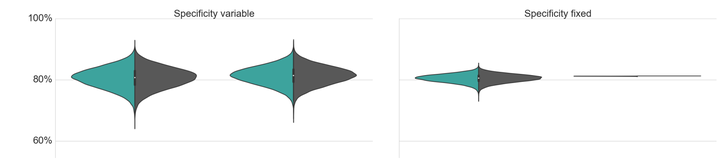


Figure 6 **T21 PPV distribution with sampling enabled or disabled for specificity (left pane/right pane), prevalence (left/right plot in pane), or sensitivity (green/gray)**

## Conclusion

- Simulation from published data enables computation of the confidence interval (CI) over NIPS PPV.
- NIPS PPV CIs are well-separated by maternal age, indicating the value of patient-specific PPV computation.
- Additional study of population prevalence could further narrow CIs.

**REFERENCES: 1.** Gregg AR. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2016 Jul 28. doi: 10.1038/gim.2016.97. [Epub ahead of print] **2.** Taylor-Phillips S. Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards, and Patau syndromes: a systematic review and meta-analysis. *BMJ* Open 6, e010002. doi:10.1136/bmjopen-2015-010002 **3.** Savva GM, Walker K, Morris JK. The maternal age-specific prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome). *Prenat Diagn*, 30: 57-64 (2010). **4.** Hecht CA and Hook HB. The imprecision in rates of Down syndrome by 1-year maternal age intervals: a critical analysis of rates used in biochemical screening. *Prenat Diagn*, 14: 729-738 (1994). **5.** Snijders RJM *et al.* Maternal age- and gestation-specific risk for trisomy 21. *Ultrasound Obstet Gynecol*, 13:167-170 (1999). **6.** Morris JK and Savva GM, The Risk of Fetal Loss Following a Prenatal Diagnosis of Trisomy 13 or Trisomy 18; *Am J Med Genet A*, 146A:827-832 (2008). **7.** Porreco RP et al. Am J Obstet Gynecol, 211(4): 365.e1-12 (2014).

**View all posters and research at**
research.counsyl.com