

## Clinical impact of additional findings detected by genome-wide non-invasive prenatal testing: Follow-up results of the TRIDENT-2 study

Van Prooyen Schuurman L. , Siermans E. A. , Van Opstal D. , Henneman L. , Bekker M. N. , Bax C. J. , Pieters M. J. , Bouman K. , de Munnik S. , den Hollander N. S. , Diderich K. E. M. , Faas B. H. W. , Feenstra I. , Go A. T. J. I. , Hoffer M. J. V. , Joosten M. , Komdeur F. L. , Lichtenbelt K. D. , Lombardi M. P. , Polak M. G. , Sarquis Jehee F. , Schuring-Blom H. , Stevens S. J. C. , Srebniak M. I. , Suijkerbuijk R. F. , Tan-Sindhunata G. M. , van der Meij K. R. M. , van Maarle M. C. , Vernimmen V. , van Zelderen-Bhola S. L. , van Ravesteyn N. T. , Knapen M. F. C. M. , Macville M. V. E. , Galjaard R. J. H. , and The Dutch NIPT consortium  
Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands

### Objective

In the TRIDENT-2 study, all pregnant women in the Netherlands are offered genome-wide non-invasive prenatal testing (GW-NIPT) with a choice of receiving either full screening or screening solely for common trisomies. Previous data showed that GW-NIPT can reliably detect common trisomies in the general obstetric population, and showed that this test can also detect other chromosomal abnormalities (additional findings). However, evidence regarding the clinical impact of screening for additional findings is lacking. Therefore, we present follow-up results of the TRIDENT-2 study to determine this clinical impact.

### Methods

For all cases with a NIPT result indicative of an additional finding in the first two years of the TRIDENT-2 study (April 2017-2019), laboratory data and perinatal outcomes were collected to determine the origin (fetal, placental, maternal) and clinical impact.

### Results

Additional findings were detected in 402/110739 pregnancies (0.36%). For 358 cases, the origin was either proven to be fetal (n=79;22.1%), (assumed) confined placental mosaicism (CPM) (n=189; 52.8%), or maternal (n=90; 25.1%). For the remaining 44 (10.9%), the origin of the aberration could not be determined. Most fetal chromosomal aberrations were pathogenic and associated with severe clinical phenotypes (61/79; 77.2%). For CPM cases, occurrence of pre-eclampsia (8.5% [16/189] vs 0.5% [754/159924]; RR 18.5), and birth weight <2.3<sup>th</sup> percentile (13.6% [24/177] vs 2.5% [3892/155491]; RR 5.5) were significantly increased compared to the general obstetric population. Of the 90 maternal findings, 12 (13.3%) were malignancies and 33 (36.7%) (mosaic) pathogenic copy number variants, mostly associated with mild or no clinical phenotypes.

### Conclusion

Data from this large cohort study provide crucial information for deciding if and how to implement GW-NIPT in screening programs, and for the challenging interpretation, counseling and follow-up of additional findings.