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# Prenatal detection of atypical chromosomal aberrations from FMF combined first-trimester screening

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## Objective

To assess the performance of combined first-trimester screening for the common trisomies (cFTS) in detecting atypical chromosomal aberrations using the FMF algorithm in a national setting with high uptake of cFTS. Further, we will estimate the potential impact of replacing cFTS with non-invasive prenatal testing (NIPT) in terms of detecting atypical aberrations.

## Methods

All pregnant women in Denmark are offered cFTS and a second-trimester scan for malformations. The uptake is high with >90% and >95% attending cFTS and the second-trimester scan, respectively. In case of a high-risk screening result or if malformations are detected, follow-up testing is offered (women in Denmark primarily opt for invasive testing with chromosomal microarray). We conducted a nationwide register-based cohort study on all pregnancies seen for cFTS between January 2008 and December 2018. Pregnancy data including biomarkers and biometries from all screening visits were retrieved from the National Danish Fetal Medicine Database (DFMD). All cytogenetic and molecular karyotypes obtained prenatally, postnatally, or following pregnancy loss or termination of pregnancy (TOP) were retrieved from the Danish Cytogenetic Central Register (DCCR). All karyotypes were categorized as pathogenic or not, and atypical pathogenic aberrations were identified (microdeletions and -duplications, unbalanced translocations, inversions, and marker chromosomes).

## Results

We included data on 565,712 pregnancies seen for cFTS of which 4.8% were screen positive (T21 risk >1 in 300 and/or T18/13 risk >1 in 150). Overall, 35,640 pregnancies (6.3%) were genetically examined; 30,464 from prenatal samples (amniocentesis or chorionic villus sampling), 2,564 from fetal tissue following pregnancy loss or TOP, and 3,202 from postnatal samples obtained before the age of two. Chromosomal aberrations were identified in 1 in 141 of the screened pregnancies (0.71%, n=4,017). Atypical aberrations made up 31% of the abnormal karyotypes diagnosed overall (21% of the abnormal karyotypes diagnosed prenatally, 23% diagnosed following pregnancy loss or TOP, and 70% of the aberrations diagnosed postnatally). Thirty-two percent of the atypical aberrations were screen positive from cFTS and 49% were detected before birth. However, the prenatal detection rate of atypical aberrations increased during the study period to 60% in the final four years (2015-2018). The median size of the atypical aberrations diagnosed was 1.4 mb and 80.2% were smaller than 5 Mb and would therefore likely not be detected from NIPT.

## Conclusion

Combined first-trimester screening identifies 32% of the pregnancies with a fetal atypical chromosomal aberration as high-risk. In the Danish setting with an additional second-trimester anomaly scan, the overall prenatal detection rate was 60% from 2015 to 2018. Approximately 80% of the atypical aberrations are smaller than 5 Mb, why replacing invasive testing with NIPT in the Danish setting would significantly reduce the prenatal detection of atypical anomalies.