A national first trimester screening program using the FMF algorithm in a public setting - still going strong after 17 years

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Objective
To describe the organization and performance of combined first-trimester screening (cFTS) using the FMF algorithm in a national setting with high uptake of cFTS during NIPT introduction.

Methods
Based on the Danish Health Authority guideline from 2004, all pregnant women in Denmark are offered cFTS free of charge. According to the FMF algorithm, the risks of trisomy 21, 18 and 13 are calculated from fetal nuchal translucency thickness, maternal age, and biomarkers free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Further, an additional second-trimester scan for malformations is offered. In case of a high-risk cFTS result (T21 risk > 1: 300 or/and T18/13 risk > 1: 150) or in case of fetal malformations, invasive sampling and genetic testing with chromosomal microarray are offered, or as an alternative non-invasive prenatal testing (NIPT). When the guideline was published, 18 departments performed prenatal screening. To monitor and ensure high and consistent quality nationwide, all departments have met annually since then to discuss results, collaboration, and possible new elements to include in the national screening program. Finally, all trisomy 21 cases including false-negative screening results are evaluated (first-trimester audit). From this nationwide collaboration, the Danish Fetal Medicine Database (DFMD) emerged. DFMD is a national clinical quality and research database with data from 2008 and covers all pregnant women scanned as a part of pregnancy care. Data in DFMD is pooled from multiple sources including the local fetal medicine databases (Astraia, Astraia GmbH, Munich, Germany) and the Danish Cytogenetic Central Register with cytogenetic data on all pre- and postnatal samples including abortions. For this abstract, we retrieved data on screen-positive rate, cFTS attendance, and trisomy 21 detection rates from the annual DFMD quality assessment reports and the annual first-trimester trisomy 21 audit reports.

Results
From 2008 to 2020, the mean proportion of Danish pregnant women attending cFTS was 93.0% (range 88.7% to 98.3%). Of these, a mean of 4.6% (range 3.6% to 5.0%) were screen positive for trisomy 21. On average, 140-155 cases of trisomy 21 were detected annually. The mean prenatal detection rate of trisomy 21 from cFTS (proportion of all pre- or postnatally detected cases diagnosed before GA 14\textsuperscript{0} weeks) was 90.1% (range 82.0% to 95.0%) and the detection rate was above 90% since 2016. Since 2018, the detection rate of trisomy 21 before GA 22\textsuperscript{0} weeks has also been recorded, with a mean of 95.8% (range 94.5% to 98.1%). After non-invasive prenatal testing (NIPT) was introduced in 2013, invasive rates dropped substantially in response to an increased NIPT uptake. However, in the following years, rates of invasive testing increased and in 2020, 71.1% of the women with a high-risk screening result had invasive testing performed and 21.0% had NIPT performed.

Conclusion
In a national setting with >90% attending cFTS and high uptake of follow-up testing after high-risk screening results (mainly invasive testing), more than 90% of all trisomy 21 cases were detected in the first trimester. An additional 5% were detected at the second-trimester scan, thus, the national trisomy 21 detection rate was approximately 95% with a constant screen positive rate below 5% through all 17 years. Future studies will assess cFTS performance in detecting atypical chromosomal aberrations.