Key Paper Summary

Non-invasive prenatal tests (NIPT): Europe's first post-market clinical follow-up study to evaluate test quality in routine clinical practice

Reference: Non-invasive prenatal testing (NIPT): Europe's first multicenter post-market clinical follow-up study validating the quality in clinical routine (Flöck A et al., Arch Gynecol Obstet; 2017; 296(5):923-928)

Background

With the introduction of new methods for high-throughput sequencing (next generation sequencing, NGS) as well as for the quantification of chromosome-specific DNA, it became possible, based on cell-free fetal DNA (cfDNA) in maternal blood, to reliably detect chromosomal disorders in the child. In Europe, this cfDNA analysis, known as non-invasive prenatal tests (NIPT), has been preferentially used since 2012 to determine fetal trisomies 21, 18 and 13 in routine clinical practice. Nowadays, NIPTs are well established in routine clinical practice.

In general, test sensitivity and specificity, which represent the basis for providing genetic counseling to patients, were determined for NIPTs within the framework of clinical studies. Yet to what extent are these study results actually confirmed in routine clinical practice?

Why is this publication important?

The post-market clinical follow-up study presented here verifies for the first time the quality of a non-invasive prenatal test (NIPT) for the autosomal trisomies 21, 18 and 13 in singleton pregnancies in routine use in clinical practice in Germany. The study results are relevant for a reliable assessment of the test quality and at the same time, they improve the data set for providing medical counseling to pregnant women in Germany.

Result: High level of test quality for trisomies 21, 13 and 18

2232 cases were documented in full and tested for trisomy 21. Of these cases, 1946 were additionally tested for trisomy 18 and 13. (Fig. 1) 84.1% of the participating pregnant women decided on NIPT because of the following primary indications:

- advanced age over 35 years
- abnormal serum parameters
- abnormal ultrasound

A total of 53 (2.4%) chromosome disorders were included in the test collective recruited. There were 44 cases of trisomy 21, five with trisomy 18, three with trisomy 13 and one case with triploidy.

Normal newborns were evaluated in a routine follow-up examination as being euploid. Miscarriages, stillbirths, abortions and malformations were assessed using the birth report and pediatric, genetic or pathological examinations. Cases without a confirming caryotyping were excluded.

The sensitivity and specificity of the NIPT investigated for trisomy 21 (43/43) and 13 (2/2) was 100%; for trisomy 18, the sensitivity was 80% (4/5) with a specificity of 99.8%. In addition, three false-positive results for trisomy 18 were registered (false-positive rate, FPR, 0.15%).

Based on the total collective of 2232 completed cases, eleven tests were not able to be evaluated. This yields a failure rate of 0.5% (11/2232). The rate of aneuploidies in this subgroup, at 27.3% (3/11), was higher than in the total collective (2.5%; 55/2232). The rate of invasive diagnostic testing was 2.6%.

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Conclusion and recommendations for practice

The NIPT used for the study, which has been available in Germany since August 2012 as the PrenaTest®, shows a very high level of test quality for fetal trisomies 21, 13 and 18 in routine clinical practice.

It additionally shows that the test has been used to date primarily in the collective with an intermedate to high risk and thus reduces the number of invasive procedures. NIPT can also to a large extent be recommended in the low-risk collective since even in this collective, two cases with trisomy 21 were correctly classified.

Of all chromosomal disorders diagnosed in the study collective, 89% (49/55) were identified by NIPT. This shows that NIPT detects a majority of the relevant chromosomal disorders and is therefore ideally suitable as a screening method for Germany. Due to the rare false-positive and false-negative test results, it can now be indicated in Germany that NIPT should only be offered in combination with a specific and qualified diagnostic ultrasound.

In the subgroup without a meaningful PrenaTest® result, aneuploidies occurred more frequently than in the total collective. Pregnant women who do not receive a meaningful test result should therefore be offered a qualified diagnostic ultrasound to assist with making a decision regarding an invasive diagnostic procedure.

In such cases, many professional organizations, such as the American College of Medical Genetics and Genomics, recommend a prompt invasive examination (Gregg AR, Skotko BG, Benkendorf JL et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016 Oct;18(10):1056-65.).

Overall, it can be summarized that the study results presented offer a very good basis for improved counseling for pregnant women in Germany.

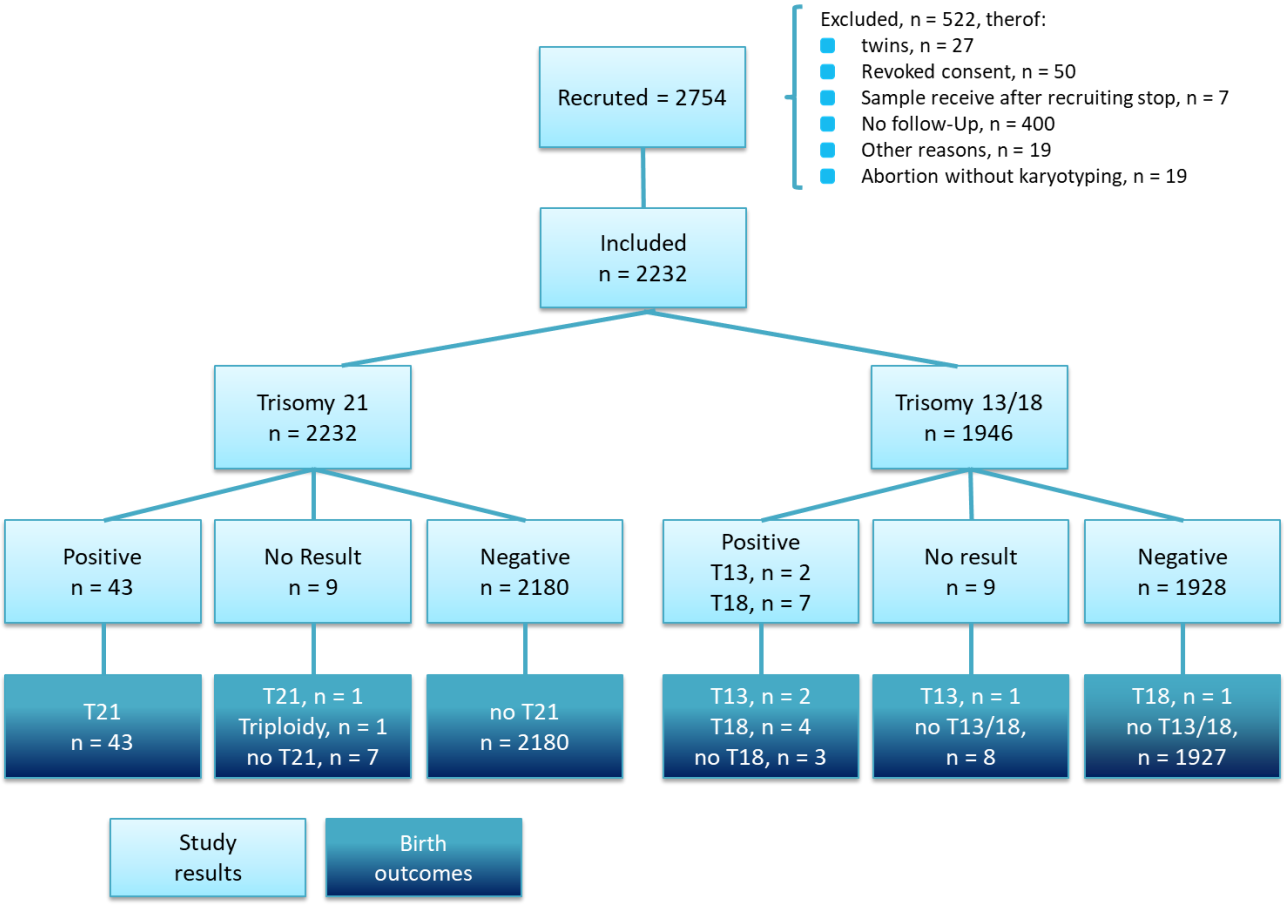

Fig.1: Study results and birth outcomes