Non-invasive prenatal testing (NIPT): Laboratory experiences of PrenaTest®

Ulrike Schöck[1], Sebastian Grömminger[1], Joachim Bonnett[1], Patricia Smerdka[1], Wera Hofmann[1]

[1] *LifeCodexx AG, Konstanz, Germany*

OBJECTIVES

Non-invasive prenatal testing (NIPT) is an emerging new option in prenatal care. According to the International Society for Prenatal Diagnosis (ISPD) NIPT is an advanced screening method for women at increased risk of common fetal aneuploidies (1). The commercially available PrenaTest® has been introduced in Europe in August 2012 with focus on Germany, Switzerland and Austria and exhibits sensitivities and specificities around 99% . The laboratory experiences from routine application of NIPT service are reported, and test accuracy, quality parameters as well as patient profiles are discussed.

METHOD

PrenaTest® for common fetal trisomies is done by massively parallel sequencing (MPS) of cell-free DNA from maternal plasma (Figure 1) (2,3). Presented data were collected during laboratory routine from August 2012 to January 2013 for the detection of trisomy 21 only, and from February 2013 onwards for the detection of trisomies 13, 18 and 21.

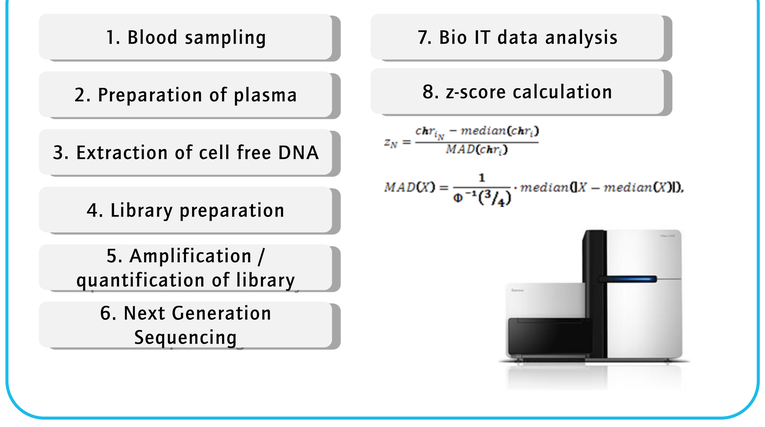
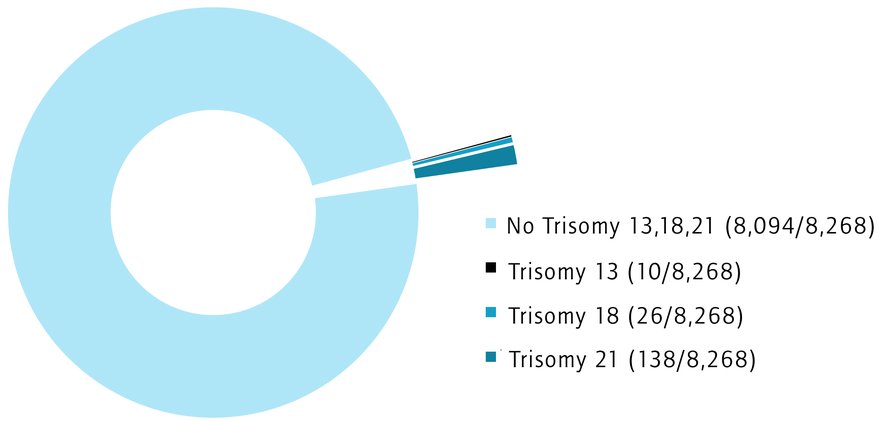


Figure 1: Analysis workflow. Median Absolute Deviation (MAD) based z-score – is computed based on the chromosomal abnormalities observed in the sample set using an euploid reference set.

RESULTS

Within the past eighteen months over 8200 successfully PrenaTest® analyses have been reported, with 98.0% negative results, 1.7% positive for trisomy 21, 0.3% positive for trisomy 18 and 0.1% positive for trisomy 13 (Figure 2). Remarkably, in the routine application the incidence of positive cases has decreased considerably in comparison to the overall incidence in the clinical trials for the PrenaTest® (from 11.6% to 2.0%) (3).

According to *ad hoc* feedback from the ordering specialists there were one false-negative result for trisomy 18 and 13 false-positive results up to now. Further analysis revealed that one discordant positive T21 case was caused by a fetus papyraceus as determined by investigation of the placenta after birth, the other discordant T21 case was reported back by the responsible doctor as a known case of a vanishing twin (4). For one discordant positive T18 case, the fetus had a euploid karyotype after amniocentesis, but placental material exhibited 80% cells with trisomy 18 in FISH analysis (confined placenta mosaic).



Discordant Results:

False positive: 2 x T21, 10 x T18, 1 x T13

False negative: 1 x T18

False Positive Rate: 0.17%

Detection Rate: 99.4%

Figure 2: Results of succesfully analysed samples using PraenaTest®

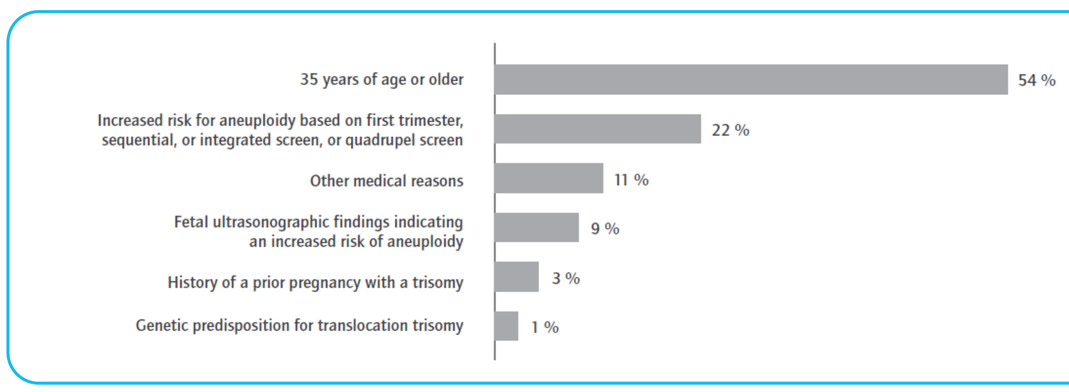


Figure 3: Summary of clinical indications for application of PraenaTest®

Currently, the main indications for the application of the PrenaTest® are an increased maternal age (54%) and an increased risk for aneuploidy based on primarily first trimester screening test (22) (Figure 3). The third important reason for doing NIPT is listed as "other medical reasons", mainly representing women with anxiety and a strong psychological need for assurance, even in the absence of indicators for a fetal trisomy.

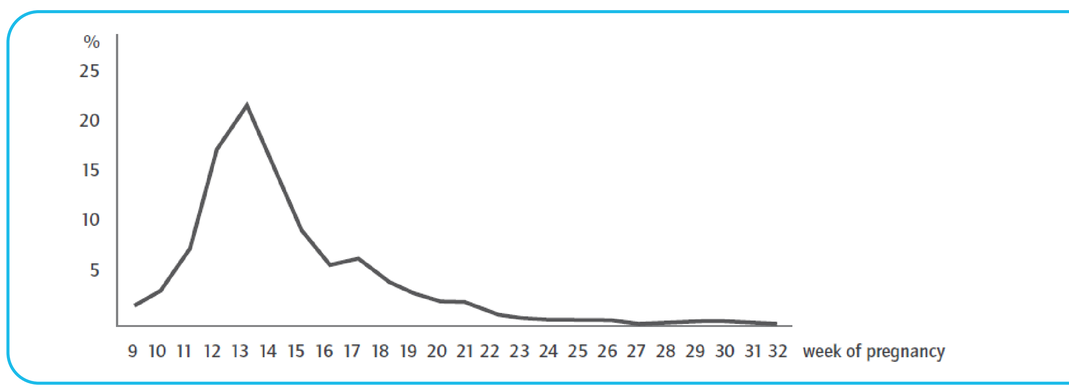


Figure 4: Overview about week of pregnancy of women who ordered PraenaTest®

Particularly women in week 12+0 through 13+6 - the period in which the nuchal translucency measurement is done - opt for the PrenaTest®. Interestingly, a second peak at week 17+0 to 17+6 is seen, which coincides with the period when amniocenteses are usually carried out (Figure 4). This might be an indication that women who would otherwise have chosen an amniocentesis to obtain information about the health of their child now select the PrenaTest®, instead.

CONCLUSION

In the near future, to characterize the limitations of NIPT more precisely, it is important to analyse thoroughly the discrepancies between NIPT results and the results of conventional karyotyping. It is intriguing that the majority of discordant results of NIPT and invasive diagnosis seem in fact to be the consequence of fetal vs. extra fetal cytogenetic discrepancies or due to undiscovered vanished twins. These findings suggest that biological reasons rather than methodical failures play the major role, emphasising the highly important collaboration between geneticists and gynaecologists specialized in ultrasonography and further analysis of discordant results.

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CONTACT

LifeCodexx AG, Dr. Wera Hofmann
w.hofmann@lifecodexx.com

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