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# qNIPT PrenaTest®

qPCR-based NIPT
for fetal trisomy 21

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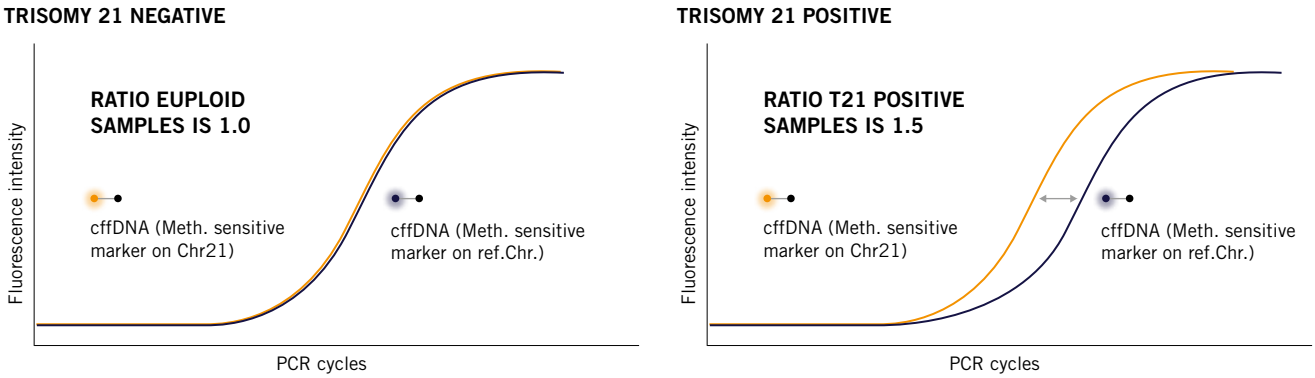
# The smart qNIPT assay

**Detection of fetal trisomy 21 based on quantitative real-time PCR**

Developed by Eurofins LifeCodexx, the smart qNIPT assay is based on quantitative real-time polymerase chain reaction (qPCR). The qNIPT determines differences in methylation patterns of specific gene regions on the maternal and fetal DNA. Certain gene regions in maternal DNA are hypo-methylated whereas the same regions are hyper-methylated in fetal DNA. These methylation specific gene regions are used as DNA biomarkers for the determination of fetal trisomy 21.

**Different qPCR signals for chromosome 21 and reference chromosome**

In an euploid case, the CP values[1] detected for chromosome 21 and reference chromosome within the same sample are rather identical, whereas in the T21 positive case the CP value for chromosome 21 is smaller. This means, that in the positive sample the crossing point is reached earlier for chromosome 21 compared to the unaffected reference chromosome. Therefore, for a T21 positive sample, the initial DNA quantity of chromosome 21 is higher compared to the initial DNA quantity of the unaffected reference chromosome. In average, chromosome 21 is 1.5 times higher concentrated, which corresponds to 3 copies of this chromosome.




Comparison of the fetal DNA of chromosome 21 and reference chromosomes for all samples on a single run.

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# Clinical performance evaluation

**Clinical performance evaluation compared to NGS-based PrenaTest®**

Following proof-of-principle and feasibility studies with around 1,500 samples, a blinded study was performed to assess the clinical performance in maternal blood samples from singleton pregnancies. The samples were blinded by an independent Contract Research Organization. After extraction of cell-free DNA and methylation-specific digestion of DNA samples, a multiplex qPCR was performed. The primary qPCR data was finally evaluated with the CE-marked PrenaTest® analysis software. Results from the qNIPT analysis and from confirmatory NGS testing were compared with PrenaTest® results using NGS.[2]

**Evaluation results**

The study results of the maternal plasma samples (n=966) demonstrated a positive percentage agreement (PPA; equates to sensitivity) of 100% (lower 1-sided 95% confidence interval of 91.8%; n=35/35) and a negative percentage agreement (NPA; equates to specificity; n=931/931) of 100% compared to NGS-based PrenaTest®. The negative predictive value (NPV) of the smart qNIPT and confirmatory NGS testing was 100% (lower 1-sided 95% confidence interval of 99.68%). The average fetal fraction of all examined blood samples was 8.1%. The qNIPT provided reliable test results in 54 blood samples with a fetal fraction below 4% and as low as 2.4%.

**qNIPT – very reliable and robust**

Our results show that our proprietary qNIPT is a very reliable and robust method suitable for clinical routine in accordance with international medical associations.[3] The assay represents a more cost-efficient solution over NGS testing and provides results in the shortest possible time. While current NIPT methods require a minimum fetal fraction of 4% in blood samples from singleton pregnancies, we demonstrated in the study that our smart qNIPT assay can be employed on blood samples with a fetal fraction of as low as 2.4%.

| Study 2016 | |
|---|---|
| Correctly classified samples | 966/966 (100%) |
| Trisomy 21 positive | 35/35 (100%) |
| Trisomy 21 negative | 931/931 (100%) |
| Sensitivity (lower 1-sided 95% CI) | 100% (91.88%) |
| Specificity (lower 1-sided 95% CI) | 100% (-) |
| NPV (lower 1-sided 95% CI) | 100% (99.68%) |

The smart qNIPT does not require a minimum fetal fraction of 4%. The fetal fraction is solely determined to clarify whether a sample is from a pregnant woman and whether fetal DNA is present at all.

1 Definition of CP value of the Lightcycler (Roche): This method identifies the crossing point (CP) of a PCR reaction as the point where the reaction's fluorescence reaches the maximum of the second derivative of the amplification curve, which corresponds to the point where the acceleration of the fluorescence signal is at its maximum.

2 LifeCodexx internal data from laboratory routine (August 2012 to September 2016).

3 ACOG 2015; ESHG/ASHG 2015; ACMG 2016; ISPD 2015; Austrian-German-Swiss Recommendations for NIPT 2016; available at www.lifecodexx.com.

4 Internal data from lab routine and clinical data based on qPCR and NGS available at www.lifecodexx.com.

5 After sample receipt in the Eurofins Biomnis laboratory. Monday to Friday, except public holidays.

# qNIPT PrenaTest®
# Safe. Rapid. Reliable.

Starting from the ninth week of pregnancy (9+0 weeks since LMP) the qNIPT PrenaTest® determines fetal trisomy 21 from maternal blood with a very high test performance. qNIPT PrenaTest® is suitable for singleton pregnancies and can be used following assisted reproduction – even if donor eggs are used. If desired, the gender of the fetus may also be determined. Results are usually available in 4 to 8 working days after sample receipt and successful quality control.

| 99% | 0.1% | <0.6% | 4 – 8 DAYS |
|---|---|---|---|
| Detection rate [4] | False positive rate [4] | No-call rate [4] | Turnaround time [5] |

**In accordance with the In-Vitro Diagnostic Directive 98/79/EC**
**First NIPT with CE-marked data analysis software**

**Performance in clinical routine**
13,683 samples were successfully analysed (as of Sept. 2018) since market launch in January 2017. The numbers are based on internal data collection from the laboratory routine and feedback from the physicians on discordant results.

| | qNIPT PrenaTest® |
|---|---|
| Prevalence T21 positive cases | 1.34% (n=184) |
| Sensitivity | 98.92% |
| Specificity | 99.99% |
| PPV | 99.46% |
| NPV | 99.99% |

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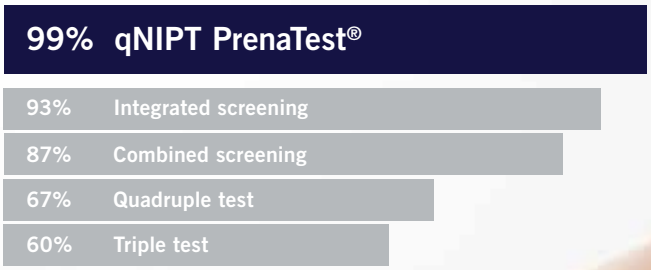
## Comparison of screening methods




Detection rates of screening methods for the determination of fetal trisomy 21 compared to qNIPT PrenaTest®[6,7]



**NIPT can be used as a primary screening method for fetal trisomy 21 in pregnant women of every age and risk group.**

Austrian-German-Swiss Recommendations for NIPT 2016[8]

**[…] any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status […]**
ACOG 2015[8]

**[…] NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS […]**
ESHG/ASHG 2015[8]

**[…] informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies […]**
ACMG 2016[8]

**[…] NIPT as a primary test can be offered to all pregnant women […]**
ISPD 2015[8]

6 Internal data from lab routine and clinical data available at www.lifecodexx.com.
7 Cuckle H, Benn P, Wright D (2005). Down syndrome screening in the first and/or second trimester: model predicted performance using meta-analysis parameters. Seminars in Perinatology 29, 252-257.
8 Recommendations of medical associations available at www.lifecodexx.com.

# Eurofins Biomnis

Eurofins Biomnis Ireland is the leading independent provider of medical laboratory testing services to healthcare organisations throughout the country, and is the exclusive provider of qNIPT PrenaTest® from Eurofins LifeCodexx in Ireland.

**Contact us at salesdept@eurofins.ie**

**www.eurofins.ie/biomnis**

**Eurofins LifeCodexx – First NIPT provider in Europe**

Headquartered in Konstanz (Germany), LifeCodexx has been developing innovative and clinically validated non-invasive prenatal tests since 2010. With the launch of the PrenaTest® in 2012, Europe's first non-invasive prenatal test (NIPT) for the determination of the most common chromosomal disorders in unborn children, LifeCodexx has been changing prenatal diagnostics considerably. Today the PrenaTest® is firmly established in many prenatal practices in Europe, the Middle East and Asia as a reliable, rapid and safe examination method. LifeCodexx was aquired by Eurofins Scientific in summer 2017, thus strengthening the group's technology portfolio in the NIPT field.

**Eurofins Biomnis and Eurofins LifeCodexx are part of:**

eurofins | Clinical Diagnostics

**Reproductive medicine by Eurofins Clinical Diagnostics**

- Present in over 70 IVF centers worldwide
- Over 650,000 tests performed per year
- From sample pick-up to medical counseling
- Clinical interpretation provided
- Accredited laboratories

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