Non – Invasive, Prenatal Testing (NIPT) for common chromosomal abnormalities

Dr. Sanli ERKAN M.D.

NIPT - Presentation Topics

- Prenatal Diagnostic Tests
- Description
- History
- Method
- Indications
- Positioning & Timing
- Summary
- Usage of NIPT wisely in real clinical practice

Prenatal Diagnostic (PND) Tests

Non - Invasive PND

- Ultrasound
- Biochemical Markers
- Molecular Genetic

NIPT

Non Invasive Prenatal Testing

Invasive PND

- Chorionic Villus Sampling
- Amniocentesis
- Chordocentesis

NIPT - Description

Primum Non Nocere !

First of all,
Do Not Harm
your patient !

NIPT - Description

Non-Invasive; it does NOT carry ANY risks to the mother or to the baby like invasive procedures.

Molecular Genetic; The quantity of cell free DNA (cfDNA) fragments circulating in maternal blood is measured by Next Generation Sequencing (NGS).

Prenatal Testing; It gives highly accurate diagnostic reports signed by Medical Geneticists with sensitivity and specificity rates of >99% for trisomies.

Non – Invasive, Molecular Genetic, Prenatal Testing NIPT

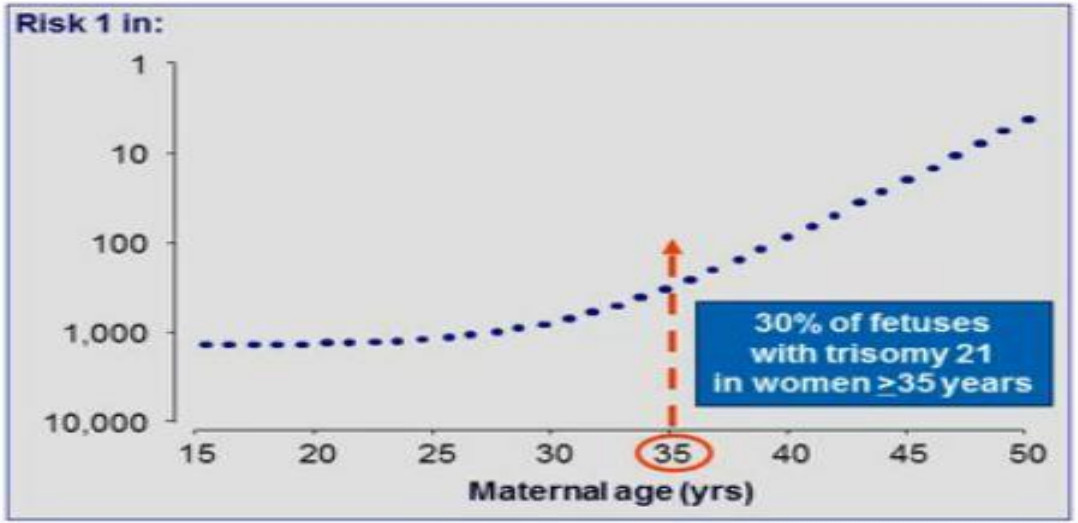
HISTORY

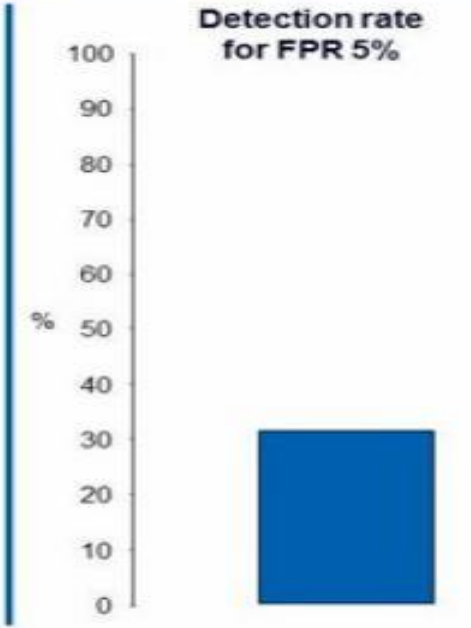
The Fetal Medicine Foundation

1970s

Screening for aneuploidies

Maternal age



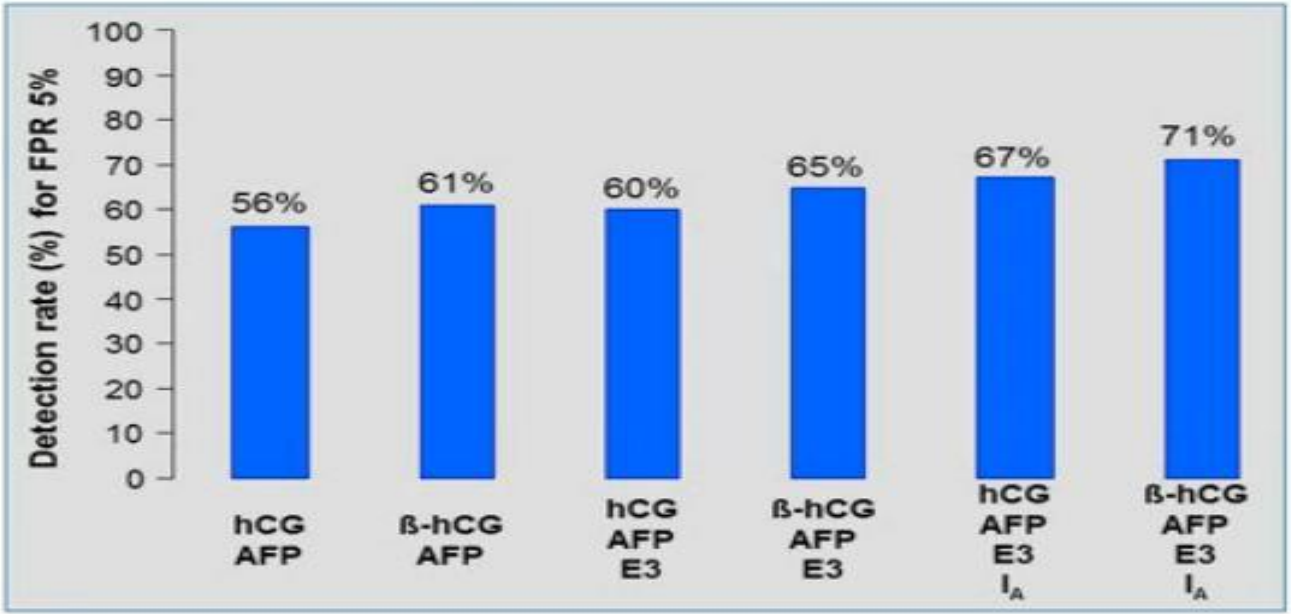


The Fetal Medicine Foundation

1980s

Screening for aneuploidies

2nd trimester biochemical testing



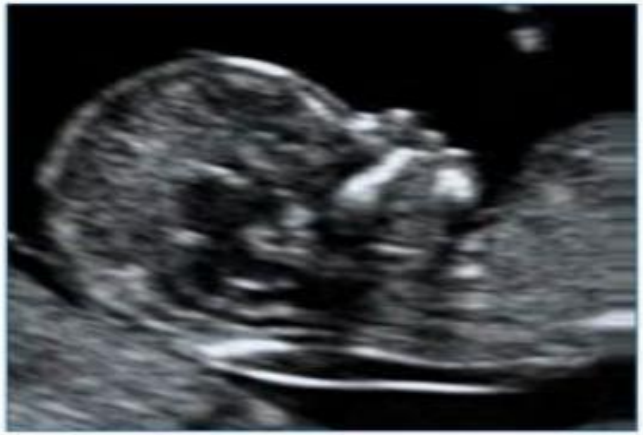
Cuckle *et al* 2005: Meta-analysis

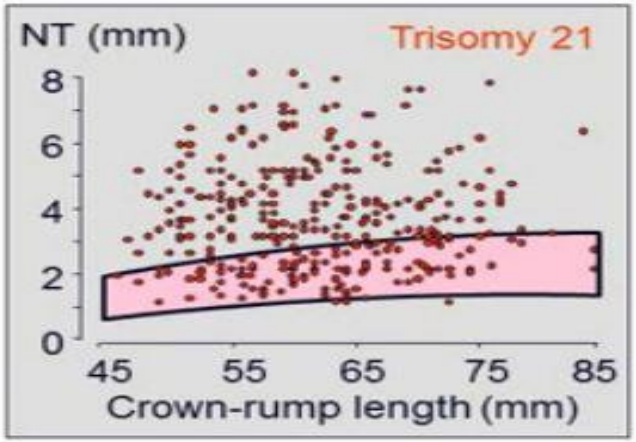
The Fetal Medicine Foundation

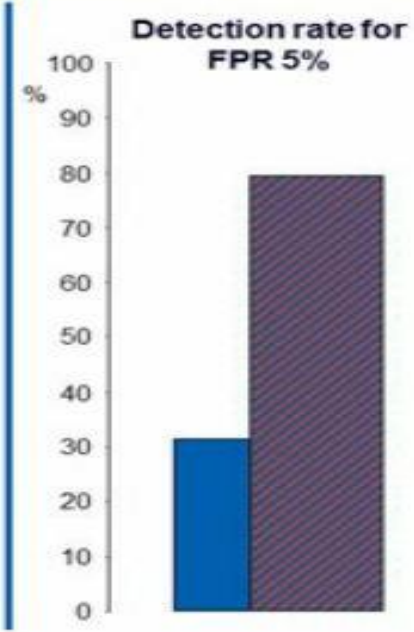
1990s

Screening for aneuploidies

Maternal age and fetal nuchal translucency





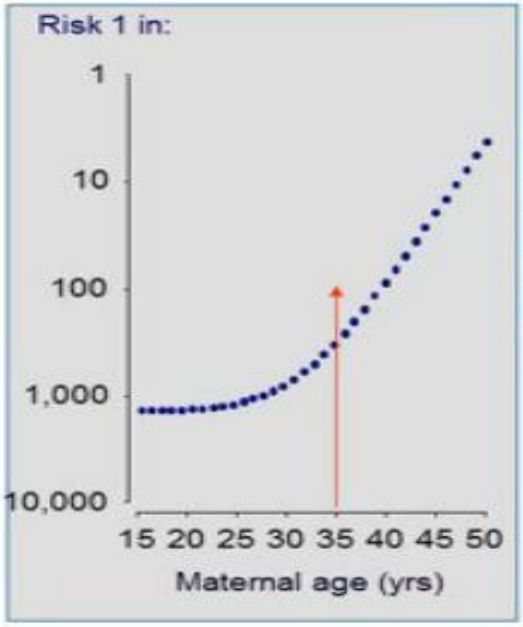


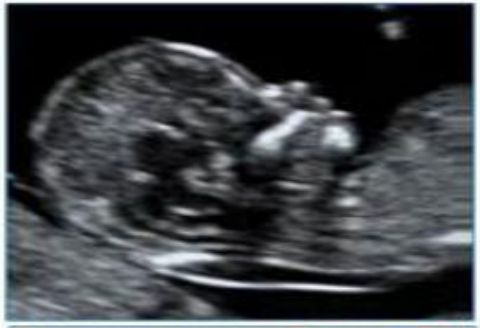
The Fetal Medicine Foundation

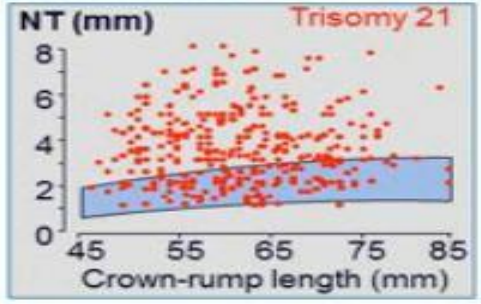
2000

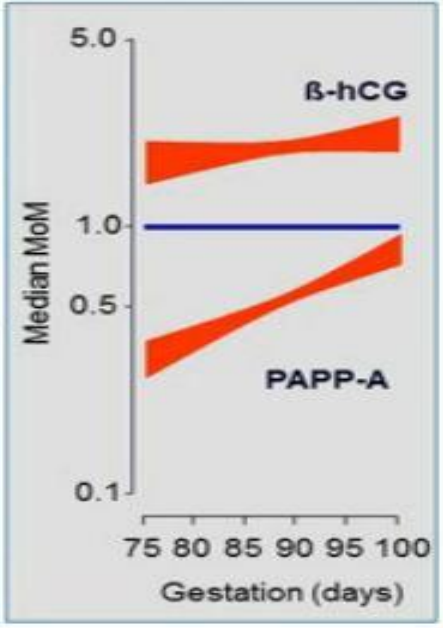
Screening for aneuploidies

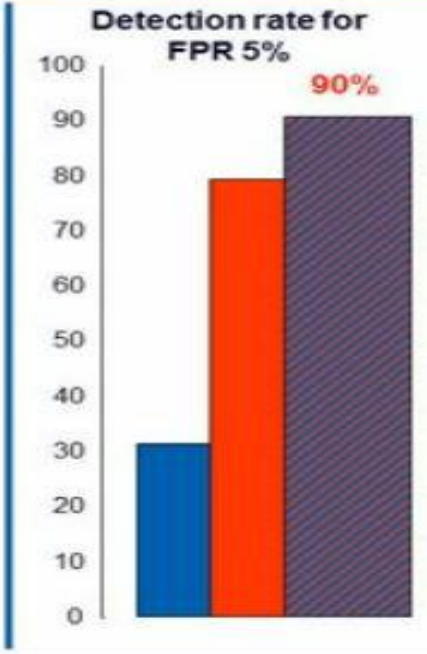
1st trimester combined test









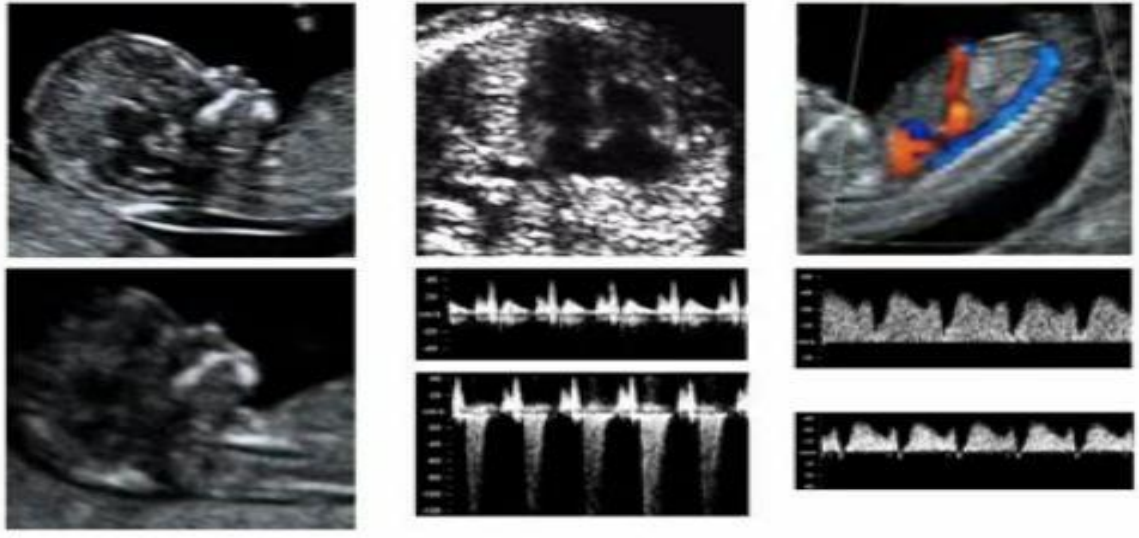


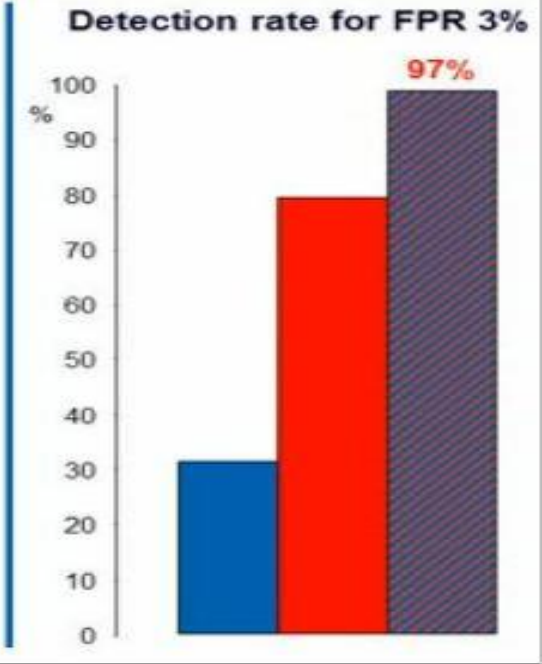
The Fetal Medicine Foundation

2000-10

Screening for aneuploidies

1st trimester combined test and additional US markers





Dennis Lo, M.D.

LEADERSHIP TEAM
BOARD OF DIRECTORS
CLINICAL ADVISORY BOARDS
DIAGNOSTICS PIPELINE

Home > About Us > Clinical Advisory Boards > Prenatal Clinical Advisory Board > Dennis Lo, M.D.

Dennis Lo, DM DPhil is the Li Ka Shing Professor of Medicine and Professor of Chemical Pathology of the Chinese University of Hong Kong. He received his BA from the University of Cambridge and his DM and DPhil degrees from the University of Oxford. He discovered the presence of cell-free fetal DNA in maternal plasma in 1997.
Since then he has been exploring the biology and diagnostic applications of this phenomenon, and has successfully developed applications of this technology for the prenatal diagnosis of fetal RhD status, monogenic diseases and fetal chromosomal aneuploidies. He serves on the Board in his capacity as a consultant to Sequenom.

SEQUENOM®

Improving Healthcare Through Revolutionary Genetic Analysis Solutions

From *Academic Research*

Through *Translational Applications*

To *Clinical Diagnostics*

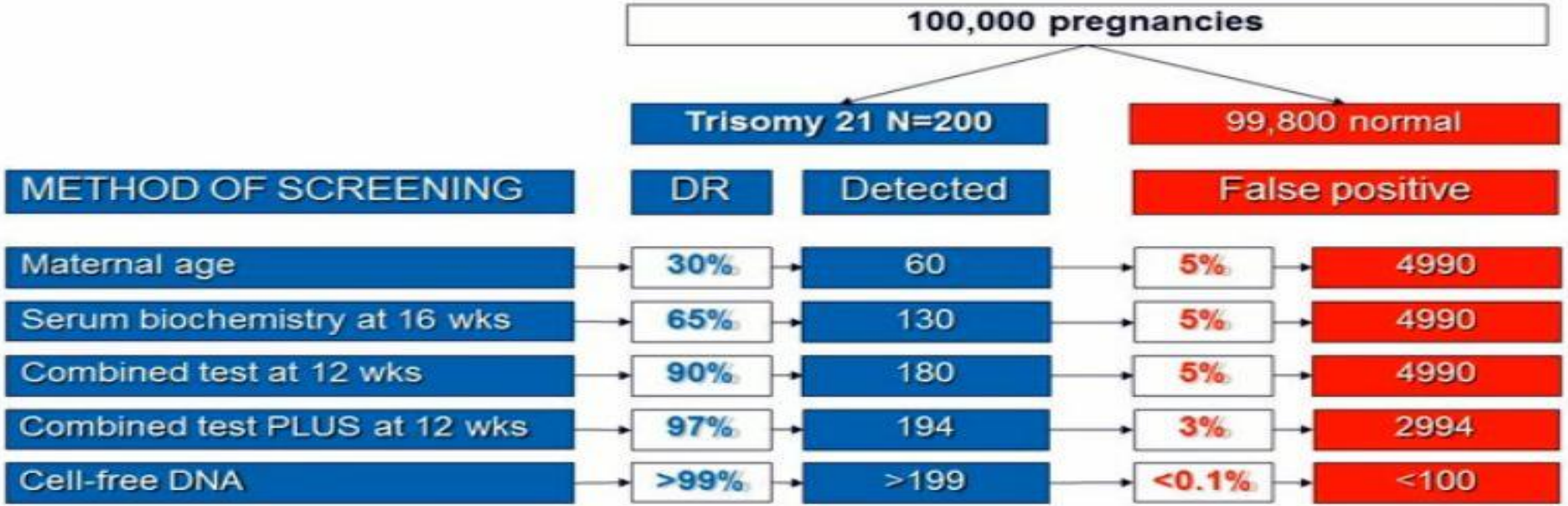
MaterniT21™ Test Commercial Launch

October 17, 2011

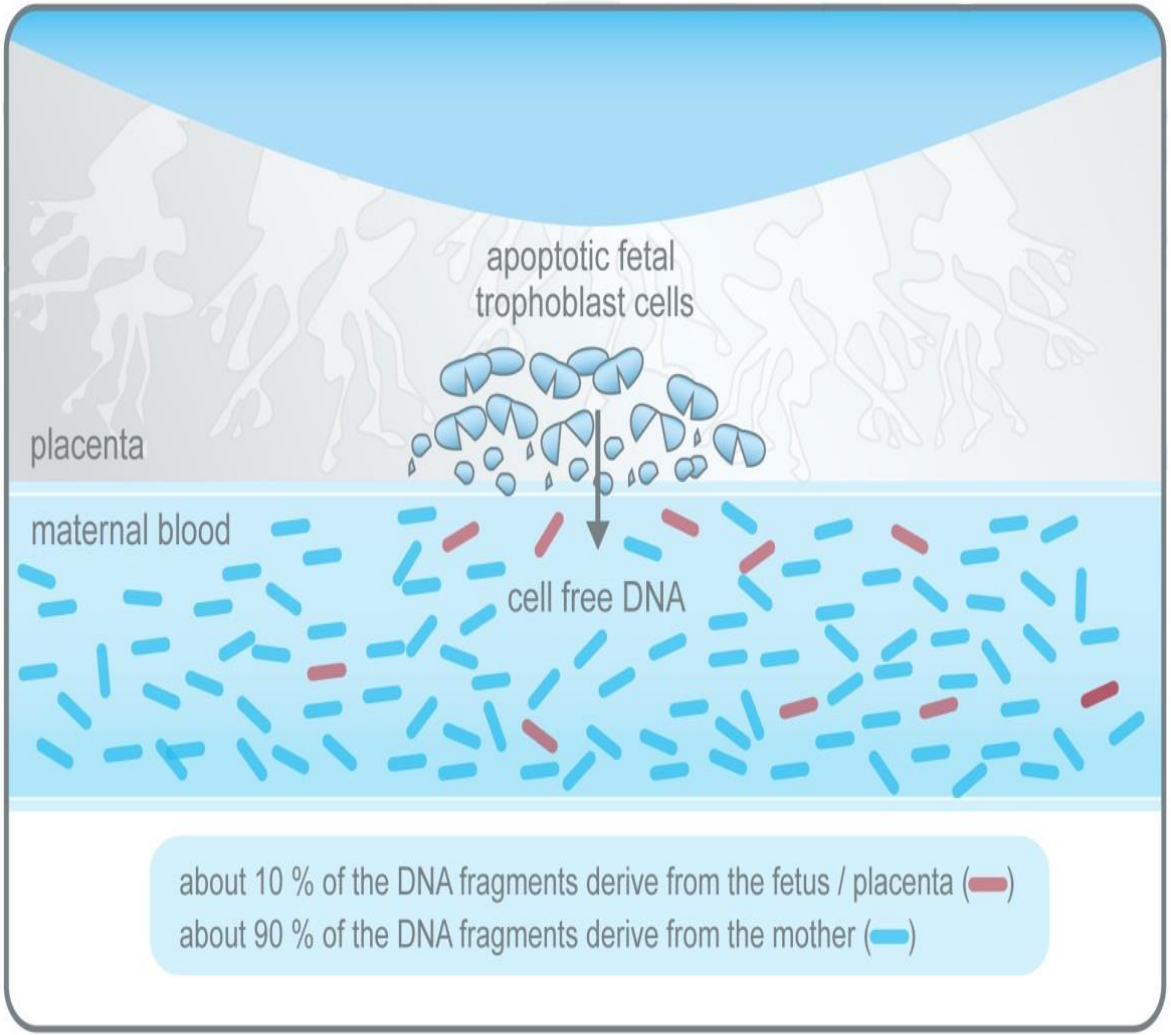
The Fetal Medicine Foundation

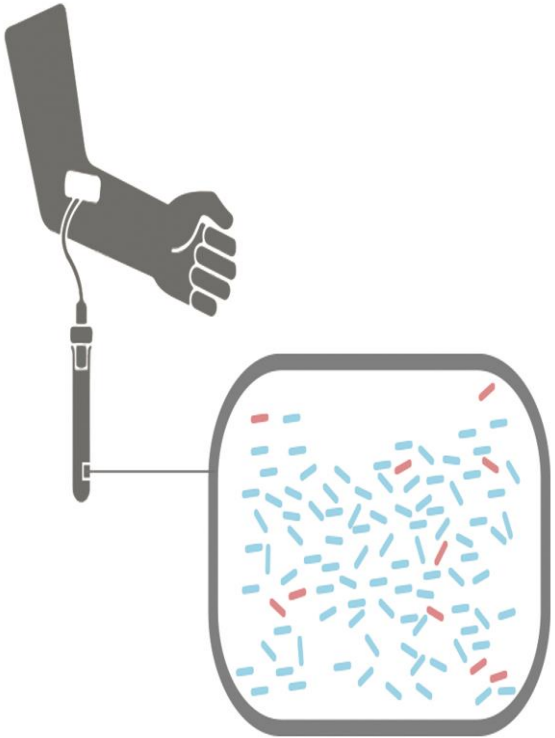
Screening for aneuploidies

Performance of screening



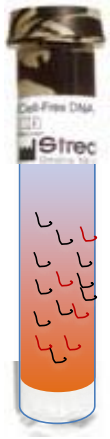
NIPT - Method


apoptotic fetal
trophoblast cells
placenta
maternal blood
cell free DNA
about 10 % of the DNA fragments derive from the fetus / placenta (—)
about 90 % of the DNA fragments derive from the mother (—)



NIPT - Method

cell free DNA
(cfDNA) separation



cffDNA
quantification

2 x 10 ml
Maternal Blood

Centrifugation

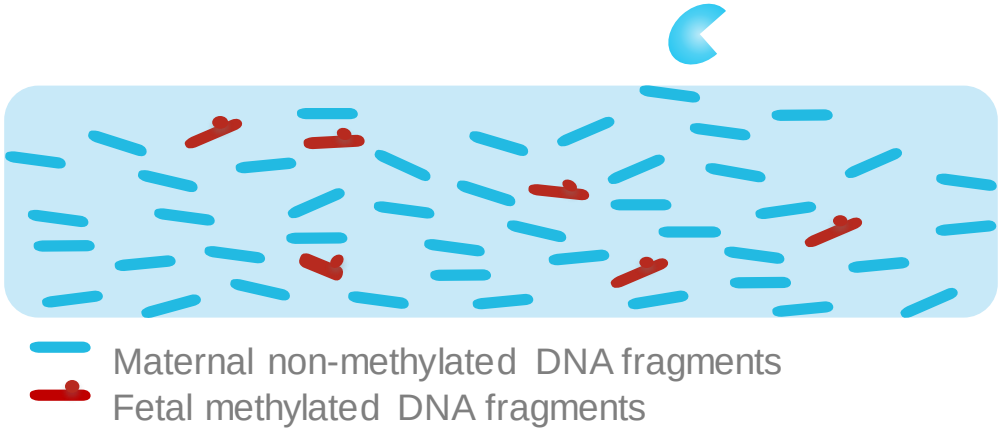
Real-time
PCR

Measurement of cffDNA content in maternal plasma

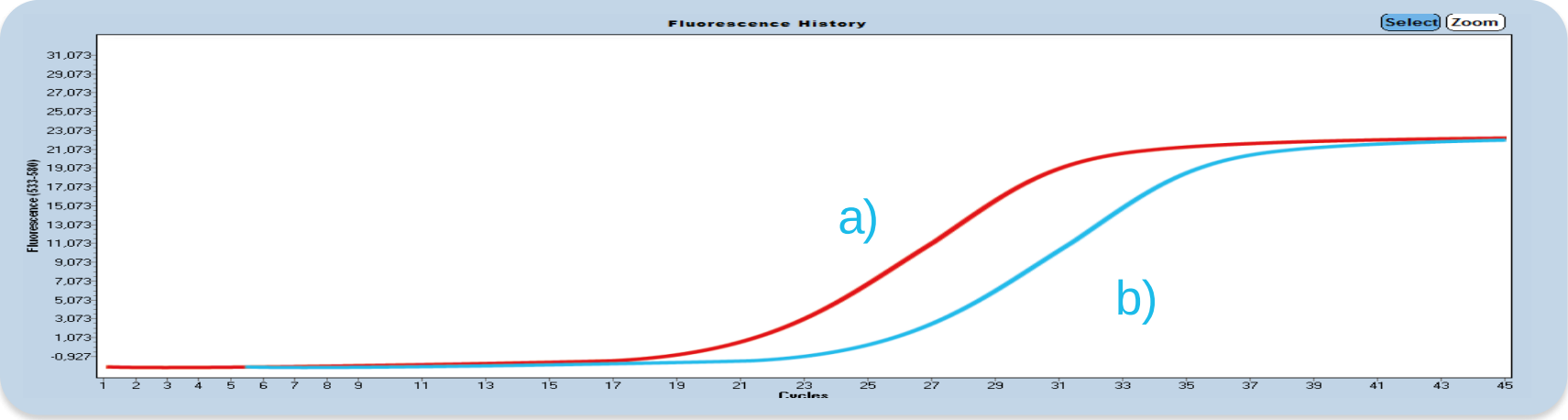
Maternal and fetal cell free DNA fragments are different in pattern;.

- maternal DNA fragments are NOT methylated,
- whereas fetal DNA fragments are methylated.

Specific enzymes digest only NOT methylated maternal DNA – fetal DNA remains intact and can be accurately measured.



Measurement of cffDNA content in maternal plasma



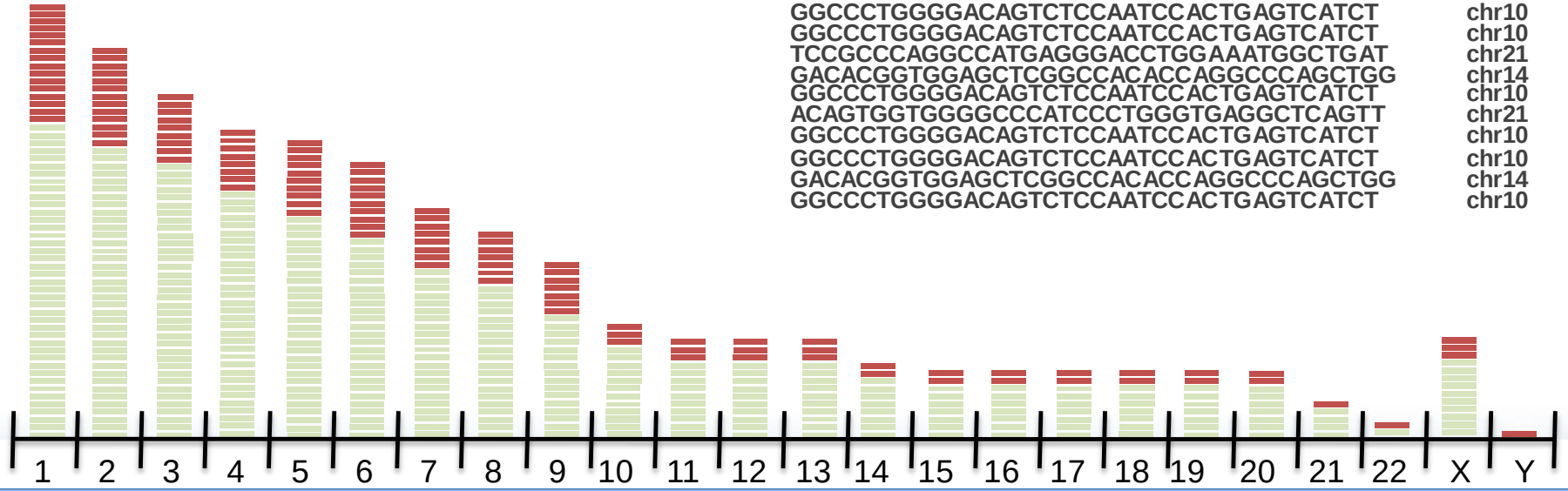
Roche

LightCycler 480 System

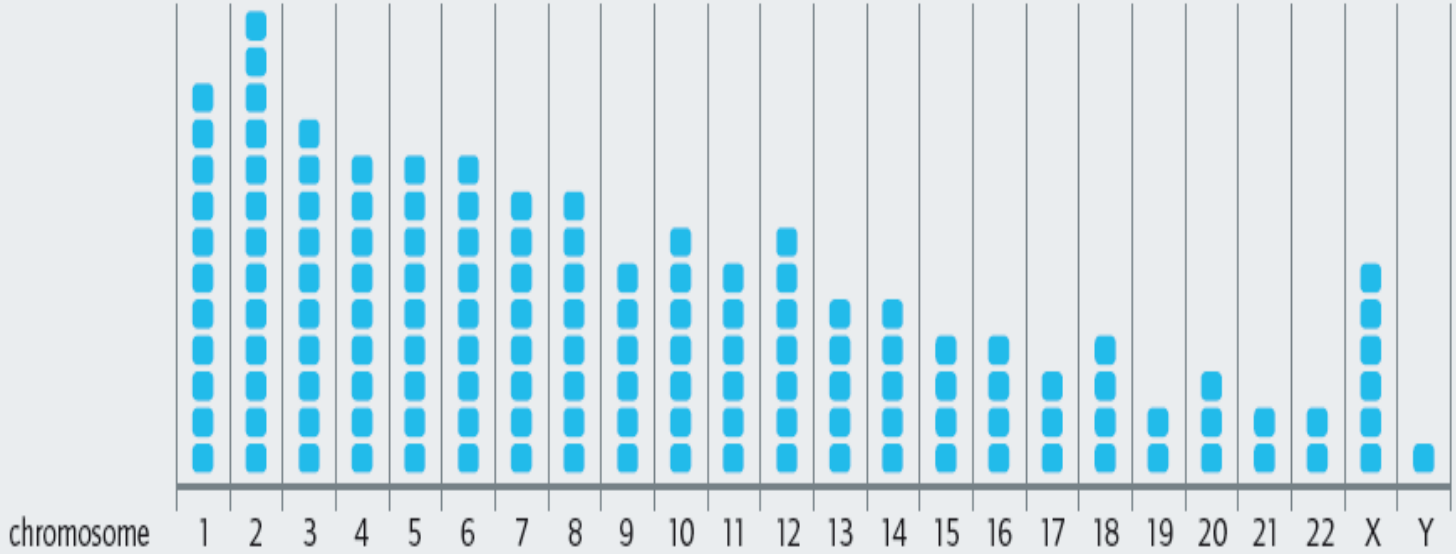
This image cannot currently be displayed.

Next Generation Sequencing (NGS)

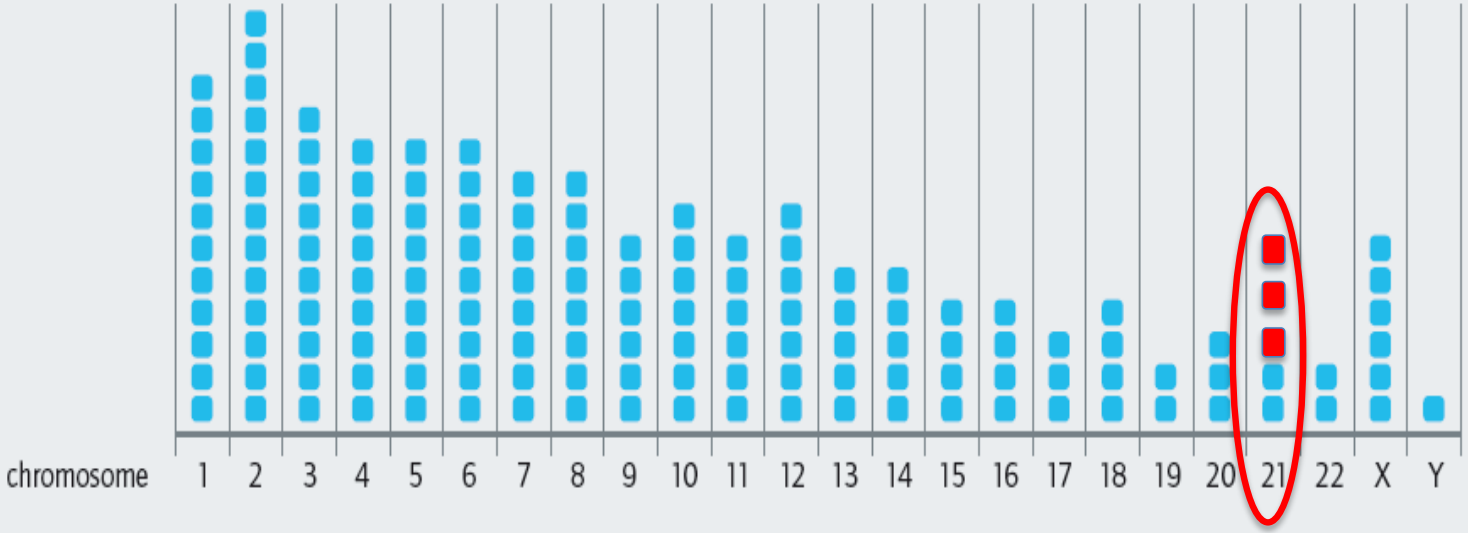
TCCGCCCAGGCCATGAGGGACCTGGAAATGGCTGAT	chr21
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG	chr14
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
ACAGTGGTGGGGCCCATCCCTGGGTGAGGCTCAGTT	chr21
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
TCCGCCCAGGCCATGAGGGACCTGGAAATGGCTGAT	chr21
GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG	chr14
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
ACAGTGGTGGGGCCCATCCCTGGGTGAGGCTCAGTT	chr21
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10
GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG	chr14
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT	chr10



Digital Karyotyping

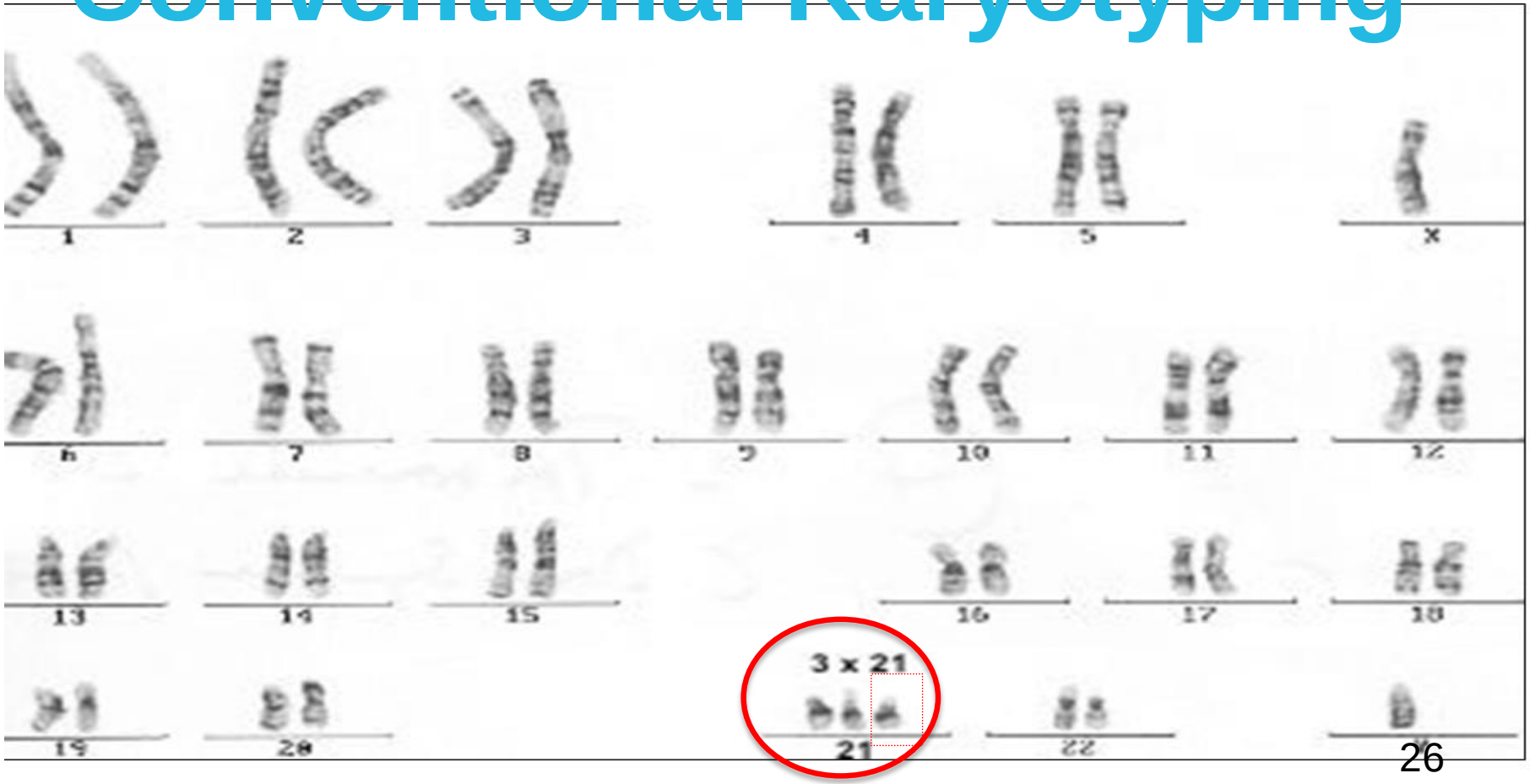


Digital Karyotyping

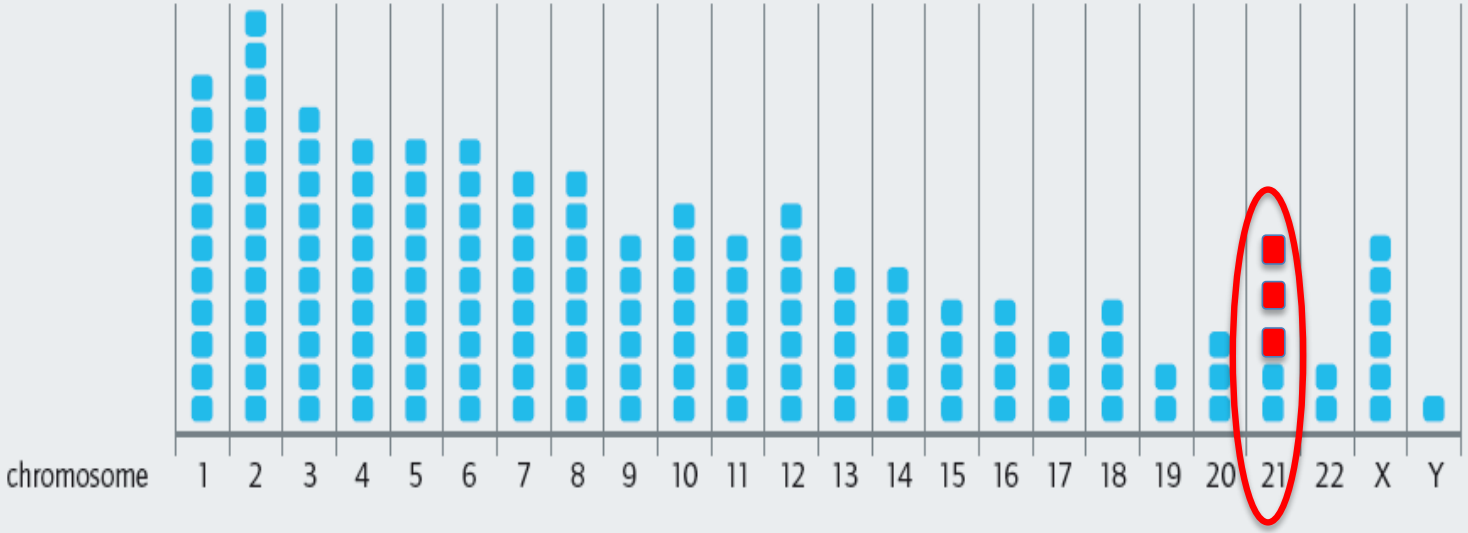


z-score **<3 Diploid** **>3 Trisomy**

Conventional Karyotyping



Digital Karyotyping



z-score **<3 Diploid** **>3 Trisomy**

NIPT - Indications

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

The Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 545 • December 2012

The American College of Obstetricians and Gynecologists Committee on Genetics

The Society for Maternal-Fetal Medicine Publications Committee

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Noninvasive Prenatal Testing for Fetal Aneuploidy

Box 1. Indications for Considering the Use of Cell Free Fetal DNA ⇦

- Maternal age 35 years or older at delivery
- Fetal ultrasonographic findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen.
- Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

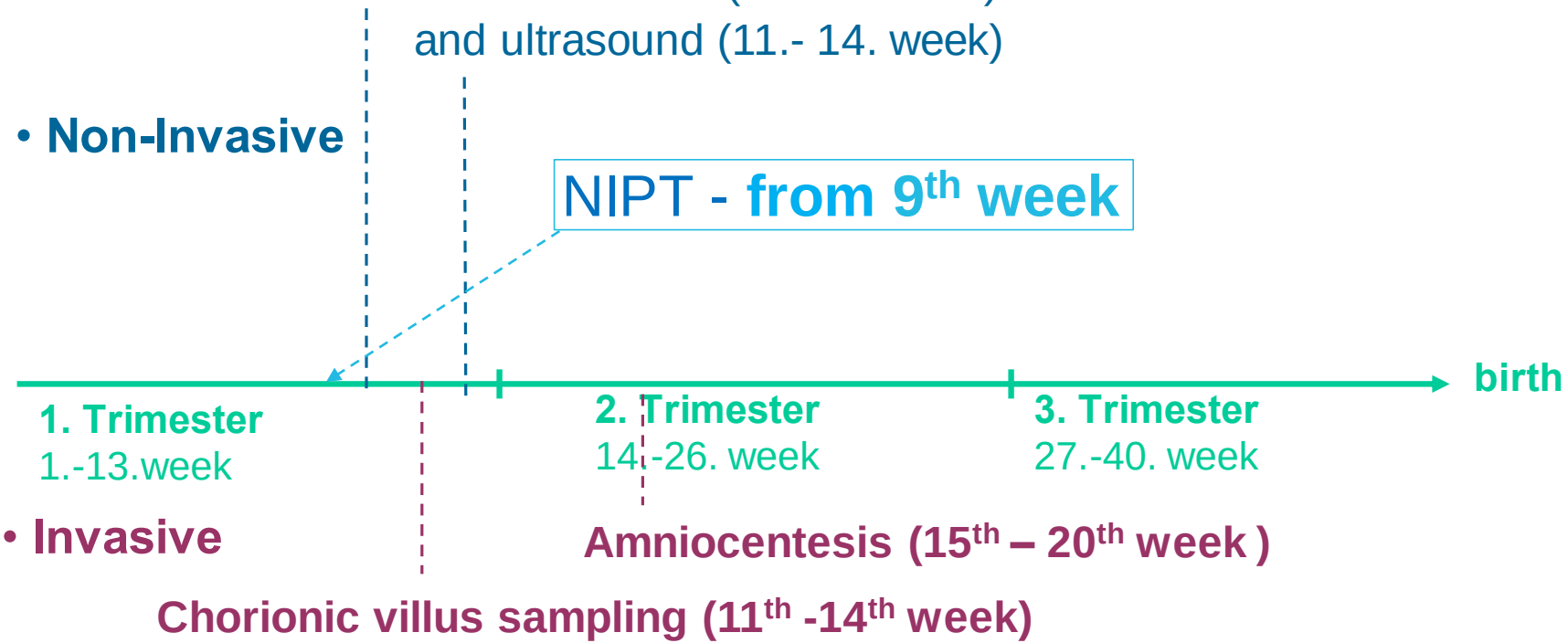
Non – Invasive, Prenatal Testing (NIPT)

POSITIONING

Positioning of NIPT during pregnancy

In combination with the 1st trimester screening
blood collection for serum marker (11.-12. week)
and ultrasound (11.- 14. week)

- **Non-Invasive**



- **Invasive**

Non – Invasive, Prenatal Testing (NIPT) for Trisomies

SUMMARY

NIPD - Summary

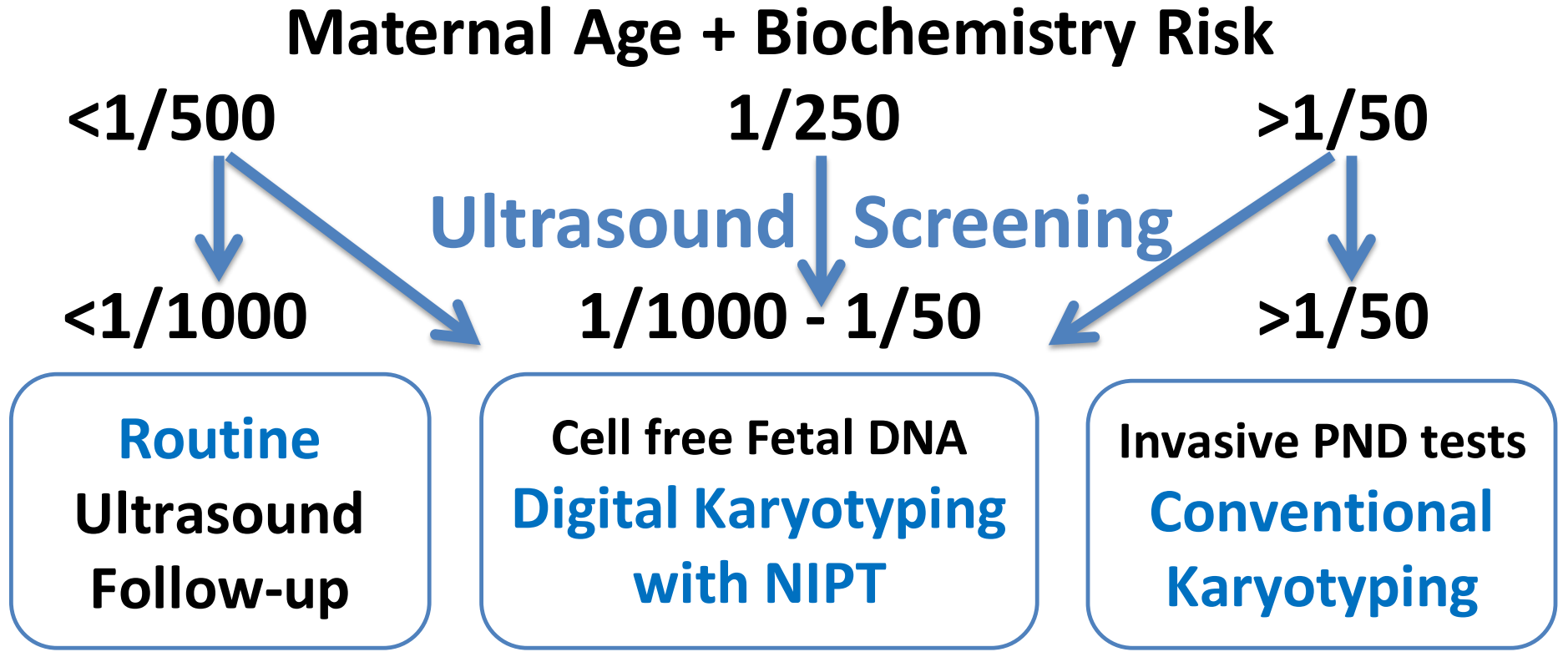
Non-Invasive; it does NOT carry ANY risks to the mother or to the baby like invasive procedures.

Molecular Genetic; The quantity of cell free DNA (cfDNA) fragments circulating in maternal blood is measured by Next Generation Sequencing (NGS).

Prenatal Testing; It gives highly accurate diagnostic reports signed by Medical Geneticists with sensitivity and specificity rates of >99% for trisomies.

Usage of NIPT wisely in real clinical practice

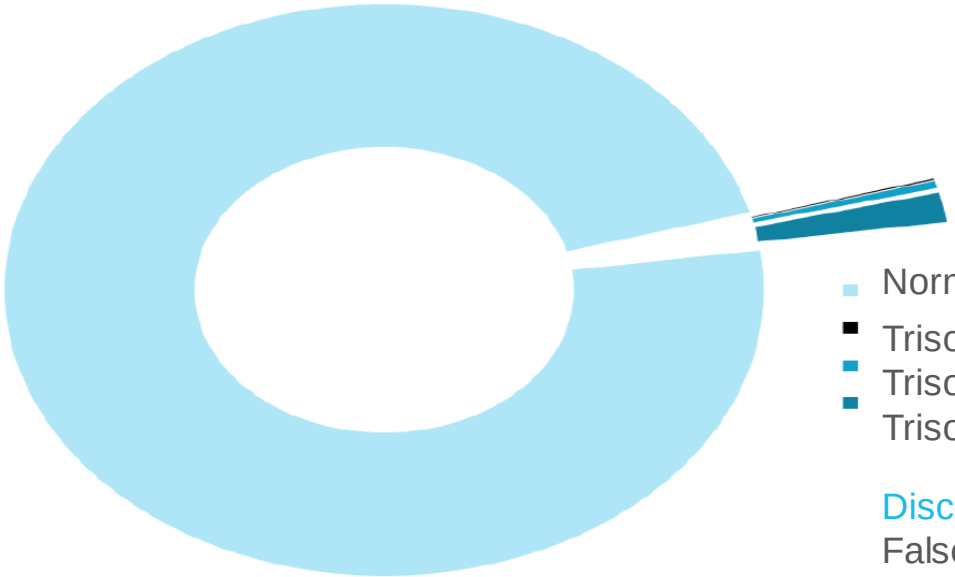
NIPT as a Reflex Test



Thank you for your attention!

High test accuracy confirmed in diagnostic routine (2014-08-31*)

- # of successfully reported samples : 13,953
- Non reportable rate: approx. 0.5% → industrial leading



* August 2012 - January 2013 Detection Trisomy 21
February 2013 - August 2014 Detection Trisomies 13, 18, 21

- Normal Range results: 98% (n= 13,657)
- Trisomie 13: 0.11% (n=16)
- Trisomie 18: 0.33% (n=46)
- Trisomie 21: 1.68% (n=234)

Discordant results :
False positive: 1 x T13, 17 x T18, 4 x T21
False negative: 1 x T13, 1x T18

- False Positive Rate (FPR): 0.16%
- Detection Rate: 99.3%

Usage of low cost NIPT in the future

NIPT as a Reflex Test