NIPT

NON – INVASIVE PRENATAL TESTING

GENDIA

Antwerp, Belgium

NIPT

NON – **I**NVASIVE **P**RENATAL **T**ESTING

Testing of cf DNA (cell free DNA)

from maternal blood during pregnancy

for fetal trisomy 21, 18 and 13

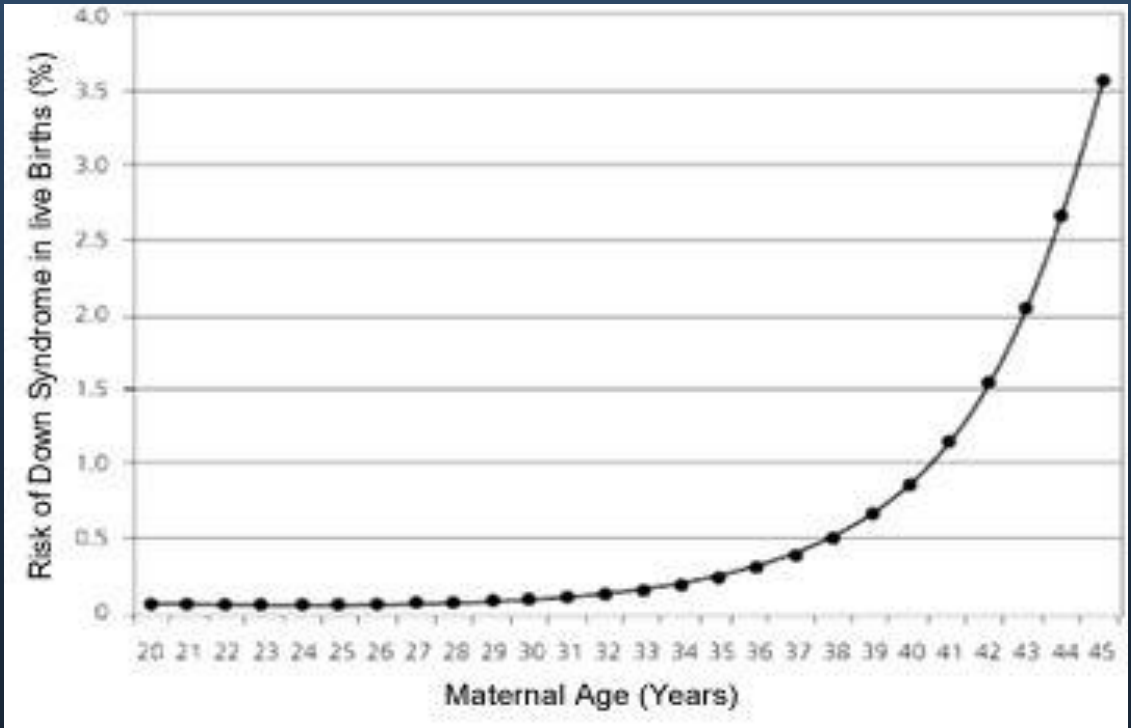
www.DOWNsyndromeNIPT.info

Frequency of fetal aneuploidies

Aneuploidy	**Syndrome**	**Frequency (**live births)
Trisomy 21	Down syndrome	1 in 700
Trisomy 18	Edwards syndrome	1 in 5,000
Trisomy 13	Patau syndrome	1 in 16,000

Risk Down syndrome versus Maternal Age

Age	Frequency (live births)
30	0.1 %
40	1 %
50	10 %



History Down syndrome screening

- 1980 : Amniocentesis (advanced maternal age)
- 1990 : Triple screening (T21, T18 and T13)
- 2000 : First trimester screening (T21, T18 and T13)
- 2012 : NIPT (T21, T18 and T13)
- 2015 : NIPT (other chromosomes, microdeletions,
- monogenic disorders)

Serum Down syndrome screening

- **Triple screening (> 1990)**
  - Maternal age
  - Serum : AFP, HCG, free oestriol
- **Combi test (> 2000)**
  - Maternal age
  - Nuchal translucency (NT)
  - Serum : free B-HCG, PAPP-A

Classical Down syndrome screening
First trimester serum screening (combi test)

Risk calculated from :

- **Maternal age :** the higher the age, the higher the risk
- **Nuchal translucency (NT) :** the higher the NT, the higher the risk
- **Serum parameters PAPP-A and free B HCG**

Classical Down syndrome screening

NT (mm)		PAPP-A (MoM)		B-HCG (MoM)	
Normal :	2.0	Normal :	1.0	Normal :	1.0
T21 :	3.4	T21 :	0.5	T21 :	2.0
T18 :	5.5	T18 :	0.2	T18 :	0.2
T13 :	4.0	T13 :	0.3	T13 :	0.5

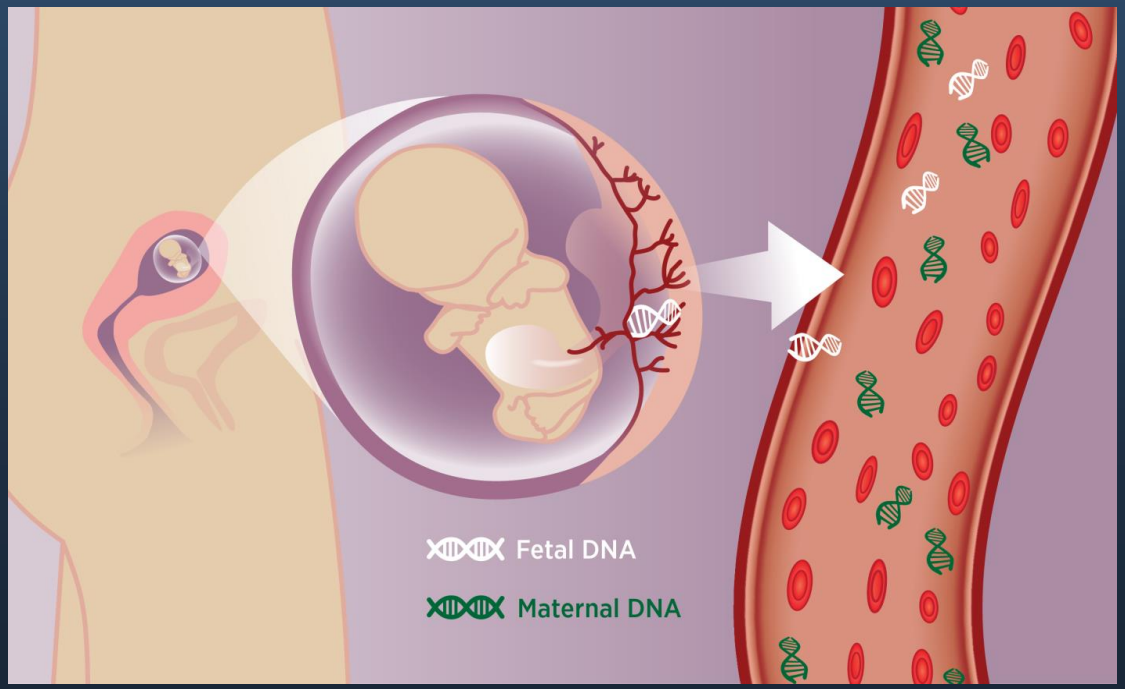
Nicolaides et al 2008

NIPT history

- 1997 : Lo et al. :cff DNA in maternal circulation
- 2001 : Fetal Rh(D) genotype
- 2006 : Sexing fetus for :
    1. X-linked genetic disorders
    2. Sexing (China)
- 2011 : Detection trisomy 21/18/13
- 2012 : > 100.000 NIPTs in USA and China
- 2015 : > 1.000.000 NIPTs in USA, Europe and China

NIPT cell-free fetal DNA (cff DNA)

- < 1 % of total DNA in maternal circulation is fetal
- 1-30 % of cell-free DNA (cfDNA) in maternal circulation is fetal



NIPT for trisomy 21

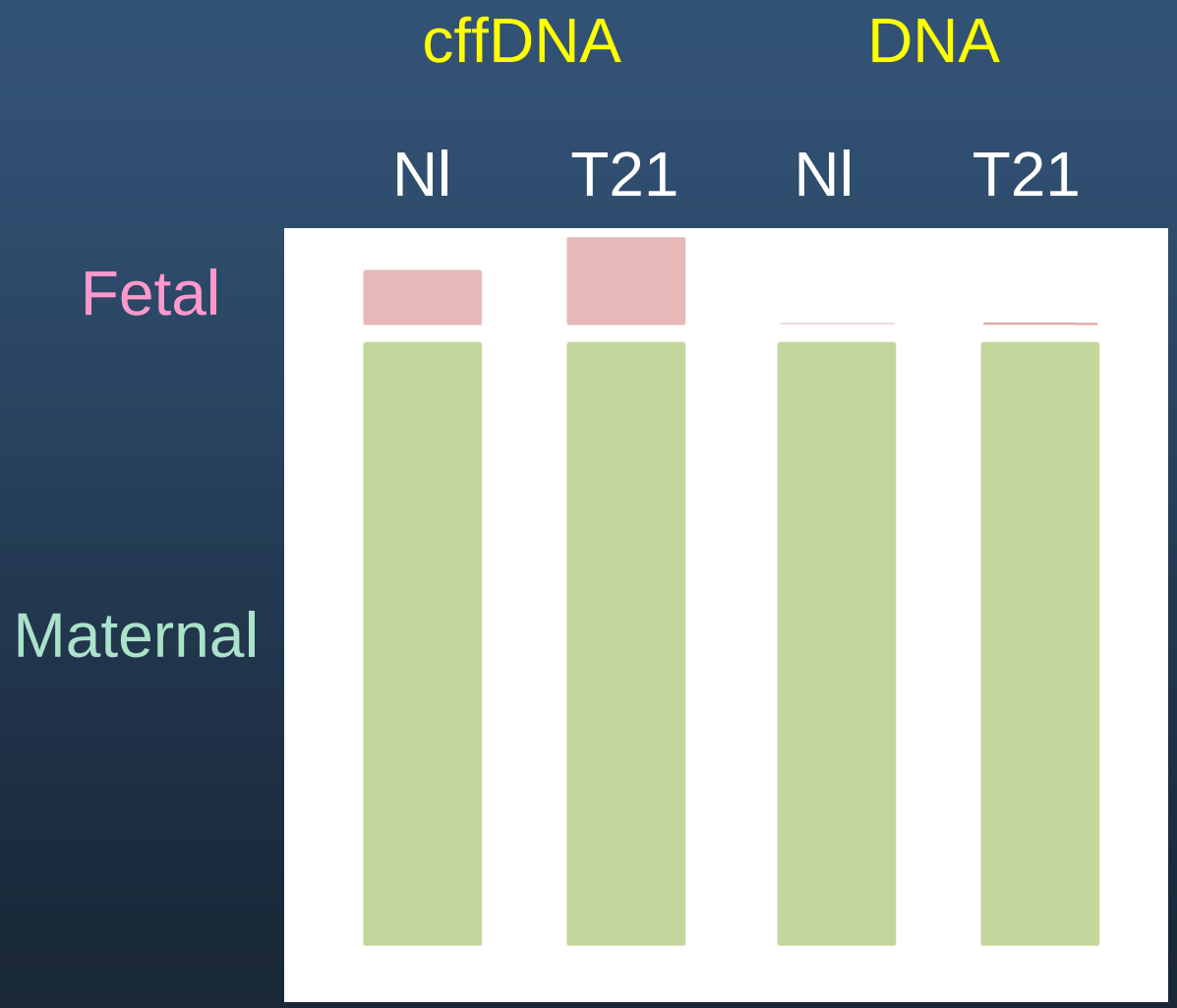
NIPT measures the ratio

of chromosome 21 signals

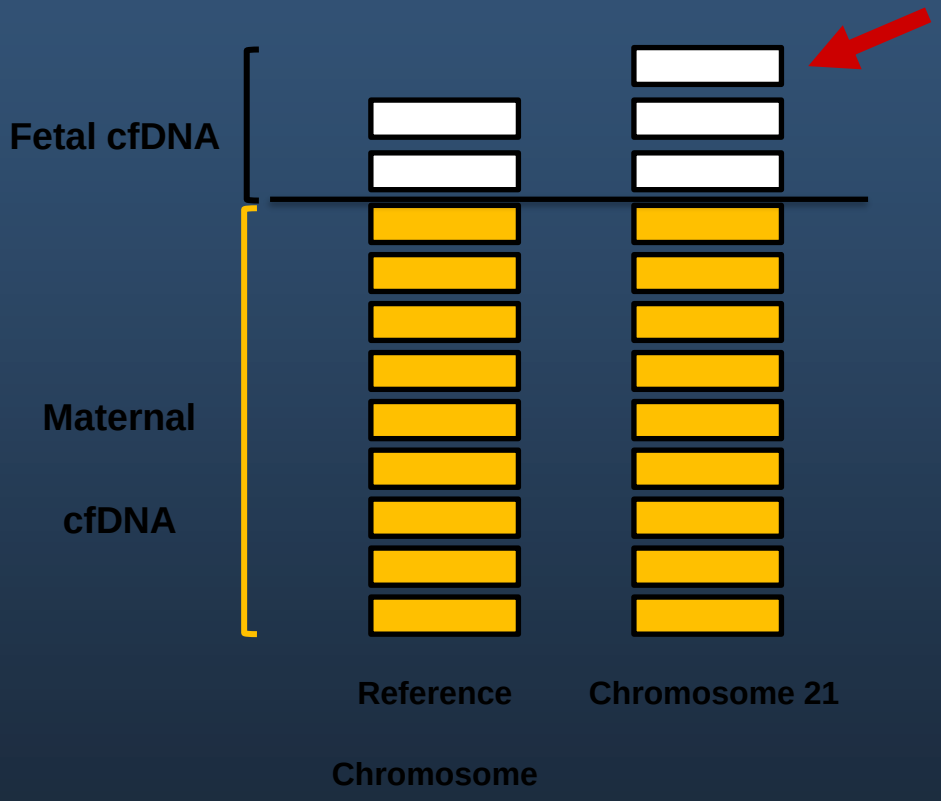
versus control chromosome signals

to exclude trisomy 21

NIPT cffDNA



Importance of fetal fraction



Fetal Fraction	Expected ratio for Trisomy
4%	1.02
10%	1.05
20%	1.10
40%	1.20

NIPT for sex aneuploidies ?

- Phenotype for sex aneuploidies is highly variable
- Mosaicism in the fetus is a problem
- Mosaicism in the mother is a problem
- NIPT for sex aneuploidies is less accurate

NIPT for other chromosomes ?

NIPT for chromosomes other than 21, 18 and 13,

microdeletions of maternal cancer is unreliable,

and should NOT be performed according to the :

- American Congress of Obstetricians and Gynecologists
- American College of Medical Genetics and Genomics
- European Society of Human Genetics
- American Society of Human Genetics
- American Society of Medical Genetics

NIPT Indications

NIPT can be performed in all pregnancies, but is certainly indicated in case of :

- Increased maternal age
- Increased risk on Combination or triple test
- Anxiety for invasive procedure (AC / CVS)

NIPT Contra indications

NIPT is NOT the test of choice when there is :

- Fetal anomalies on ultrasound
- A triplet pregnancy
- Known genetic anomalies that cannot be diagnosed by NIPT

NIPT Advantages versus combi test with AC / CVS

- High sensitivity (few false-negatives)
- High specificity (few false-positives)
- Non-invasive : no fetal risk
  - CVS : Risk of miscarriage : 1-2 %
  - AC : Risk of miscarriage : 0.5 %

NIPT Disadvantages

- Failure rate : < 1 %
- Specific blood tubes (eg Streck)
- Not available everywhere

NIPT results

1. Normal result : no specific follow up necessary,
unless ultrasound examination of the fetus reveals anomalies

2. Test failure : in < 1% pregnancies not enough fetal DNA

3. Abnormal NIPT result : confirmation by amniocentesis or chorion biopsy

Reliability NIPT versus classical Down syndrome screening

	Classical	NIPT
False negatives	20 %	3 %
False positives	5 %	< 0.1 %

NIPT : the future

1. Array CGH
   - All chromosomes
   - Small deletions - duplications

2. Detection common monogenic mutations
   - CF, Thalassemia, sickle cell

3. Whole exome / genome sequencing

NIPT essentials

1. **TEST :** trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome). Also sex of the fetus is determined, upon request.

2. **SAMPLE:** Specific test kit provided by GENDIA

3. **TIMING:** From week 11

4. **TURNAROUND TIME:** 1 week

5. **RELIABILITY:** > 99% for trisomy 21

6. **INDICATIONS:** Although NIPT can be performed in every pregnancy, it is especially indicated:
   - If the triple test or first trimester screening indicates an increased risk
   - Advanced maternal age
   - Anxiety for invasive procedures

7. **CONTRAINDICATIONS:** NIPT is not the test of choice when there is :
   - Fetal anomalies on ultrasound
   - Severely elevated NT (nuchal translucency < 3.5 mm) with normal PAPP-A and free B HCG
   - A triplet pregnancy

How offer NIPT to your patients ?

1. Refer to the consultation :

   Email : NIPT@GENDIA.net to ask for an appointment

2. Take blood yourself with our sample kit :

   Email : NIPT@GENDIA.net to ask for kits

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