Université Paris Cité

imagine
INSTITUT DES MALADIES GÉNÉTIQUES

Value of CMA in pregnancies with high risk of isolated trisomy 21 (>1/50) retrospective cohort study

Réseau AChro-Puce

Dr Helyett OLLIVIER
Gynécologue-obstétricienne
he.ollivier@wanadoo.fr

Necker
ENFANTS MALADES
HÔPITAL UNIVERSITAIRE

Unité de recherche de rattachement :
URP7328 PACT *Fédération pour la Recherche en Explorations et Thérapeutiques Innovantes in Utero* associée à l'Institut Imagine. Hôpital Necker-Enfants-Malades, Paris, France

Invasive testing or CF DNA: what to do in high risk women?

Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis

M. M. GIL*, M. S. QUEZADA*, R. REVELLO*, R. AKOLEKAR*† and K. H. NICOLAIDES*†

*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; †Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, Kent, UK

Clinical utility of expanded non-invasive prenatal screening and chromosomal microarray analysis in high-risk pregnancy

X. ZHU[1,2,3#], M. CHEN[4#], H. WANG[5#], Y. GUO[3], M. H. K. CHAU[1,2], H. YAN[4], Y. CAO[1,6], Y. K. Y. KWOK[1], J. CHEN[4], A. S. Y. HUI[1], R. ZHANG[5], Z. MENG[5], Y. ZHU[5], T. Y. LEUNG[1,2,6], L. XIONG[5], X. KONG[3] and K. W. CHOY[1,2,6]

Does a High-Risk (>1/50) Result for First-Trimester Combined Screening Always Entail Invasive Testing? Which Patients from This Group Might Benefit from cfDNA Testing?

Rocío García-Jiménez [1], Irene Valero [1], Isabel Corrales-Gutiérrez [2,3,*], Reyes Granell [1], Carlota Borrero [3,4] and José Antonio Sainz-Bueno [3,4,*]

Cell-Free DNA Testing: What Is the Reason Why High-Risk Women Choose It?

Leticia Benítez-Quintanilla[a] Montse Pauta[b] Isabel Matas[a] Irene Madrigal[c] Antoni Borrell[a, b]

[a]BCNatal, Department of Obstetrics and Gynecology, Hospital Clínic de Barcelona, Barcelona, Spain; [b]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), BCNatal Fetal Medicine Research Center, Barcelona, Spain; [c]Servei de Bioquímica i Genètica Molecular, CDB, Hospital Clínic de Barcelona, Barcelona, Spain

Is cell-free fetal DNA testing a safe option for women in a high-risk population after combined first-trimester testing?

Matthieu Dap[a,b,*], Lucie Caffin[a], Estelle Perdriolle-Galet[a], Céline Bonnet[c], Olivier Morel[a,d]

[a] Obstetrics and fetal medicine Unit, CHRU of Nancy, Nancy, France
[b] Department of fetopathology and placental pathology, CHRU of Nancy, Nancy, France
[c] Department of Genetics, CHRU de Nancy, Vandœuvre-lès-Nancy, France
[d] Inserm, Diagnostic and Interventional Adaptive Imaging, University of Lorraine, Nancy, France

In France, an invasive examination is proposed to patients at high risk of trisomy 21

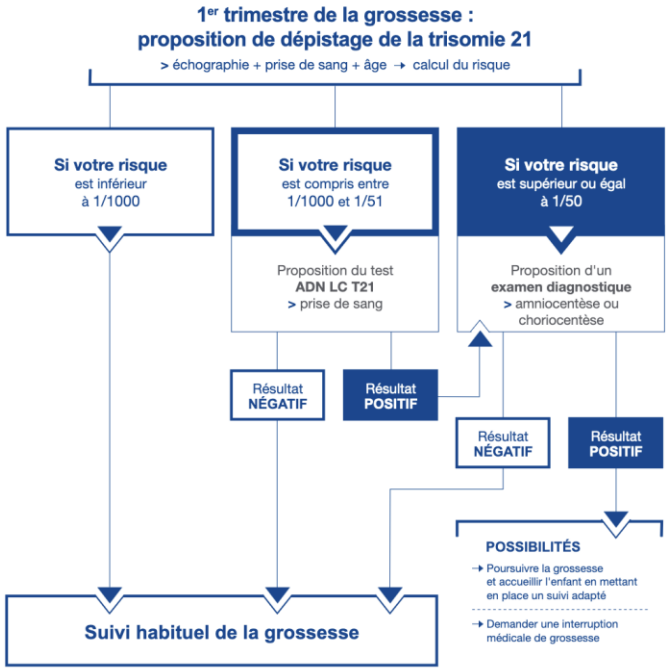
- What **chromosomal abnormalities** are found when doing chromosomal microarray (CMA)?
- **Detectable** using **CF DNA**?

- Aims:

  →*Chromosomic abnormalities diagnosed*

  →*Factors associated with chromosomal imbalance CMA*

  →*Could have been seen at CF DNA?*

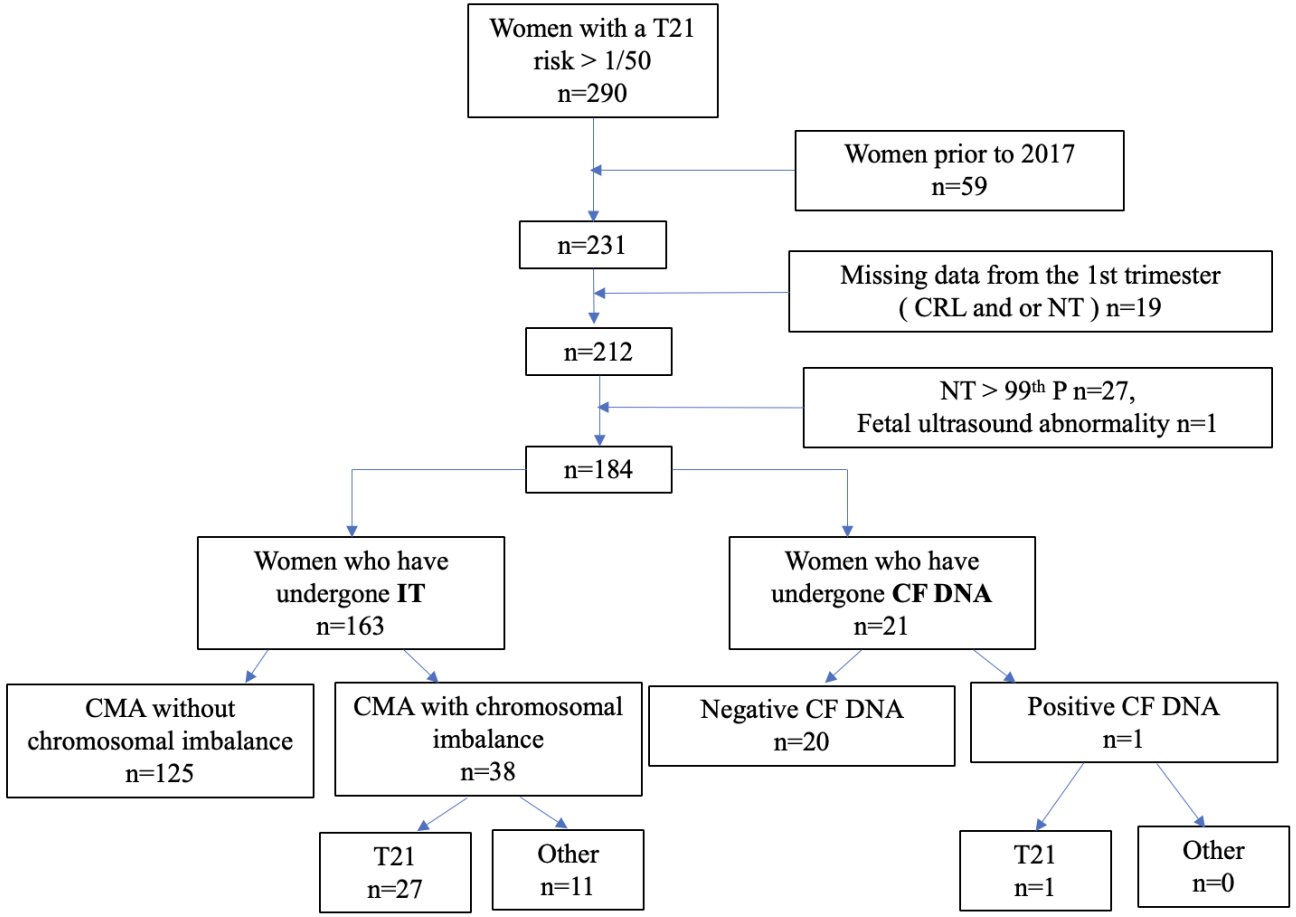


www.has-sante.fr

Materiel and methods

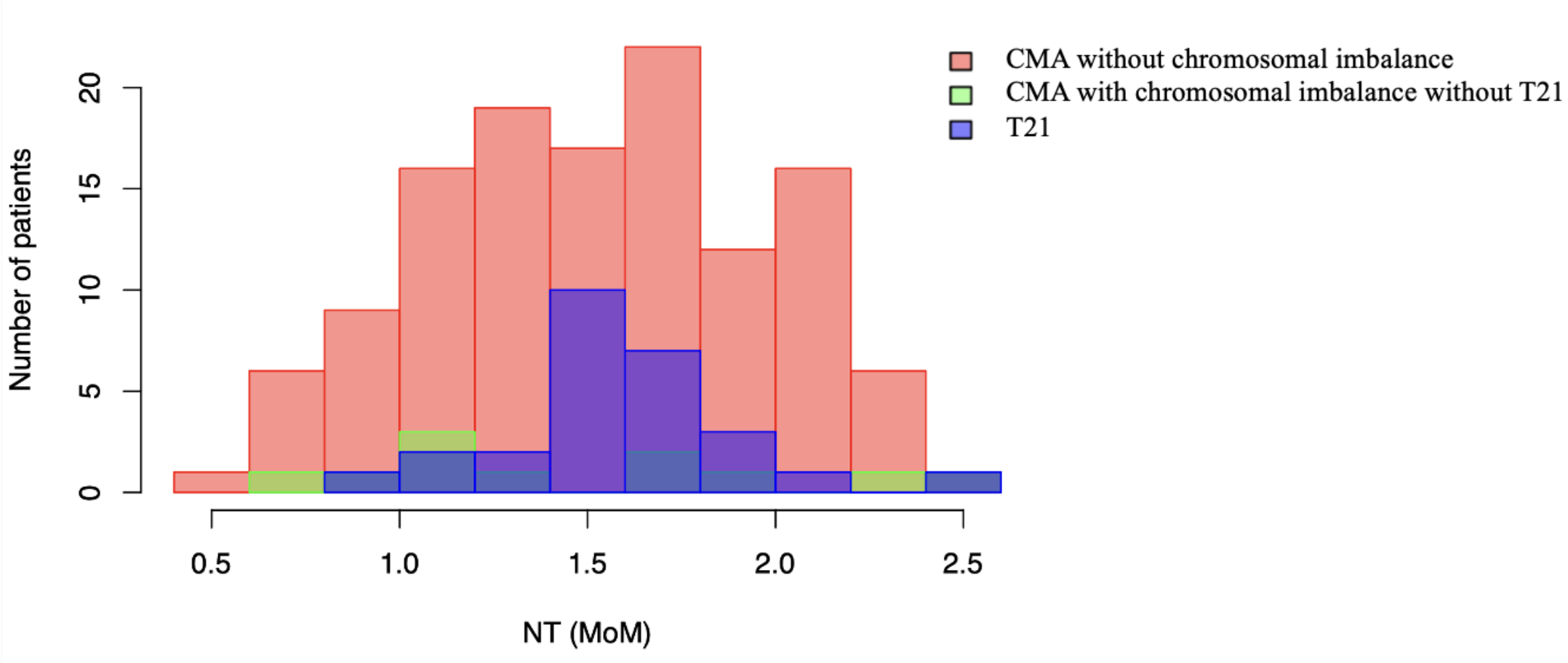
- Retrospective study at Necker hospital
- January 2017 to June 2023
- High risk women > 1/50
- **No ultrasound abnormality**

- 89% acceptability rate for IT



Flowchart of the study

An even distribution of neck thickness in the three populations



Results 1/3: Chromosomal abnormalities detected by CMA

	Maternal age (y)	NT (mm)	Risk	HCG (MoM)	PAPP-A (MoM)	Invasive testing		Gestational age at the time of invasive testing (WG)	TOP	Intrauterine death	Living birth	Average weight (g)	Gestational age at birth (WG)	Genetic abnormality identified
						CVS	Amniocentesis							
Aneuploidy other than T21														
Case number 1	46	2	30	0.15	0.16	1		12.4	1	0	0		13.6	**Trisomy 18**
Case number 2	39	2.9	10	0.59	0.29		1	16	1	0	0		16.6	**Trisomy 18**
Case number 3	35	1.5	10	6.41	0.25		1	17	1	0	0	435	22.4	**Mosaic trisomy 22 (AF 20%)**
Case number 4	34	2.95	35	0.91	0.37		1	18,5	0	0	1	3225	39	**CVS: 45,X AF: Mosaic monosomy X (85%)**
Case number 5	35	1.8	30	3.92	0.08		1	16.1	0	1	0			**AF: Mosaic trisomy 16 (AF 8%)**
Case number 6	36	2	12	4.87	0.25	1		14	0	0	1	950	28.6	**CVS: CVS 47,XY,+16 AF: Mosaic trisomy 16 (AF 10%)**
Confined placenta mosaicism														
Case number 7	39	3.1	10	1.3	0.89	1		12.3	0	0	1	3350	41.6	**Confined placental mosaicism for trisomy 2 (50%)**
Case number 8	33	3.3	18	1.01	0.9	1		12.1	Null	Null	Null	Null	Null	**Confined placental mosaicism for trisomy 13 (5%)**
CNV (Copy Number Variant)														
Case number 9	40	2.9	10	3.77	1.54	1		13.3	0	0	1	2000	35	**4q35.1q35.2 deletion inherited from the father (2.6 Mb), class 2**
Case number 10	43	1	40	4.6	0.9		1	16.3	0	0	1	2200	37	**6q15q16.1 deletion inherited from the father (2.1 Mb), class 2**
Case number 11	35	1.7	29	4.76	0.59		1	21.4	1	0	0	645	24.5	**CVS: triploidy (direct examination) culture failure AF: absence of triploid cells, de novo 2q31.1 deletion (13.9 Mb) class 5**

	Chorionic Villus Sample				Amniocentesis			CMA	Type of fetoplacental mosaicism
	Direct examination		Cell culture						
	Karyotype	FISH	Karyotype	FISH	Karyotype	FISH	CMA		
True Fetal Mosaicism (TFM)									
Case number 3	**47,XY,+22**	Not performed	**47,XY,+22**	Not performed	**mos 47,XY,+22[4]/46,XY[10]**	Not performed	Not performed	**arr(22)X3** Uncultured chorionic villi	**TFM VI**
Case number 4	**45,X**	Not performed	**45,X**	**45,X.nuc ish(DXZ1x1,DYZ3x0)**	**45,X**	**nuc ish(DXZ1x1) [85/100]**	**arr(X)x1[0.85]**		**TFM VI**
Case number 5	*Patient seen in the second trimester*				Not performed	**nuc ish(contig 16ptel,contig 16qtel)X3[8/100]**	**arr(16)X3[8/100]**	**arr(16)X3[8/100]**	
Case number 6	**47,XY,+16**	Not performed	*Failed culture*		Not performed	**nuc ish(contig16ptelx3,contig16qtelx3) [85/100]**	**arr(16)X3[8/100]**	**arr(16)X3** **Uncultured chorionic villi**	
Confined Placental Mosaicism (CPM)									
Case number 7	46,XY	Not performed	**mos 47,XY,+2[10]/46,XY[10]**	Not performed	Not performed	ish(D2ZX2) [200]	arr(1-22)X2,(X,Y)X1 Uncultured Amniotic Fluid	arr(1-22)X2,(X,Y)X1 Uncultured Amniotic Fluid	**CPM II**
Unclassifiable									
Case number 8	**46,XY, ish mos 13(RB1X3) [5/100].arr(X,Y)X1,(1-22)X2**	Not performed	Not performed	ish X (DXZ1x1),Y(DYZ3x1),13(RB1x2)	*The patient has chosen not to undergo amniocentesis*			arr(X,Y)X1,(1-22)X2 Uncultured chorionic villi	

Results 1/3: Genetics abnormalities detected by CMA: 3 CNV detected: **only one pathogenic CNV (0,6%)**

	Sample type	CMA results	Deletion size (Mb)	Inheritance	Pathogenicity According to Rigg's classification of the CNV
Case number 9	AF	arr[GRCh37] 4q35.1q35.2(185787209_188405222)x1	2.6	pat	Class 2
Case number 10	AF	arr[GRCh37] 6q15q16.1(91598727_93720602)x1	2.1	pat	Class 2
Case number 11	AF	arr[GRCh37] 2q31.1q32.1(172809441_186659690)x1	13.9	dn	Class 5

Results 2/3: lower **PAPP-A** in CMA with chromosomal imbalance

CMA without chromosomal versus CMA with chromosomal imbalance

Characteristics	CMA without chromosomal imbalance n=125[1]	CMA with chromosomal imbalance n=38[1]	p-value[2]	Overall, n=163[1]
Maternal age (y)	39 (35.0,41.0)	39.0 (35.0, 41.0)	0.8	39.0 (35.0, 41.0)
NT (MoM)	1,58 (1.19, 1.92)	1.54 (1.31, 1.79)	0.8	1.57 (1.22, 1.83)
HCG (MoM)	1.78 (1.21, 3.30)	2.00 (1.39, 3.88)	0.2	1.88 (1.22, 3.22)
PAPP-A (MoM)	0.71 (0.45, 1.12)	0.44 (0.27, 0.68)	<0,001	0.63 (0.37, 1.07)
Average weight (living birth) (g)	3180 (2805, 3500)	3225 (2200, 3350)	0.4	3180 (2801, 3498)
Gestational age (WG)	39.10 (38.15, 40.53)	38.0 (35.5, 40.58)	0.5	39.05 (38.00, 40.58)

[1]Median (IQR)

[2]Wilcoxon rank sum test

CMA without chromosomal imbalance CMA with T21

Characteristics	CMA without chromosomal imbalance n=125[1]	T21 n=27[1]	p-value[2]	Overall, n=152[1]
Maternal age (y)	39 (35.0,41.0)	40.0 (36.5, 41.5)	0.4	39.0 (35.8, 41.0)
NT (MoM)	1,58 (1.19, 1.92)	1.54 (1.47, 1.75)	0.5	1.58 (1.25, 1.85)
HCG (MoM)	1.78 (1.21, 3.30)	1.99 (1.59, 3.11)	0.2	1.87 (1.23, 3.20)
PAPP-A (MoM)	0.71 (0.45, 1.12)	0.45 (0.38, 0.64)	0.001	0.64 (0.38, 1.08)
Average weight (living birth) (g)	3180 (2805, 3500)	3410	0.7	3180 (2832, 3500)
Gestational age (WG)	39.10 (38.15, 40.53)	20.55 (10.28, 30.83)	0.8	39.10 (38.05, 40.58)

→ *Placental insufficiency in aneuploidies?*

Results 3/3: **55%** of abnormalities would have been detected

	Genetic abnormality identified n=11	Would have been seen at the extended CF DNA >7Mb
Case number 1	**Trisomy 18**	**Yes**
Case number 2	**Trisomy 18**	**Yes**
Case number 3	**CVS: 47,XY,+22 AF: Mosaic trisomy 22 (20%) (TFM VI)**	**Yes**
Case number 4	**CVS: 45,X Mosaic monosomy X (85%) (TFM VI)**	**Yes**
Case number 5	**Patient seen at 2nd semester AF: Mosaic trisomy 16 (8%)**	**?**
Case number 6	**CVS 47,XY,+16 AF: Mosaic trisomy 16 (10%)**	**Yes**
Case number 7	Confined placental mosaicism for trisomy 2 (50%) (CPM II)	No
Case number 8	Confined placental mosaicism for trisomy 13 (5%) (Probably CPM I)	No
Case number 9	4q35.1q35.2 deletion inherited from the father (2.6 Mb), probably benign CNV	No
Case number 10	6q15q16.1 deletion inherited from the father (2.1 Mb), probably benign CNV	No
Case number 11	**De novo 2q31.1 deletion (13.9 Mb), pathogenic CNV**	**Yes**

Results 3/3: **45%** of abnormalities would not have been detected

	Genetic abnormality identified n=11	**Would have been seen at the extended CF DNA >7Mb**
Case number 1	Trisomy 18	Yes
Case number 2	Trisomy 18	Yes
Case number 3	CVS: 47,XY,+22 AF: Mosaic trisomy 22 (20%) (TFM VI)	Yes
Case number 4	CVS: 45,X Mosaic monosomy X (85%) (TFM VI)	Yes
Case number 5	***Patient seen at 2nd semester*** **AF: Mosaic trisomy 16 (8%)**	**?**
Case number 6	CVS 47,XY,+16 AF: Mosaic trisomy 16 (10%)	Yes
Case number 7	**Confined placental mosaicism for trisomy 2 (50%) (CPM II)**	**No**
Case number 8	**Confined placental mosaicism for trisomy 13 (5%) (Probably CPM I)**	**No**
Case number 9	**4q35.1q35.2 deletion inherited from the father (2.6 Mb), probably benign CNV**	**No**
Case number 10	**6q15q16.1 deletion inherited from the father (2.1 Mb), probably benign CNV**	**No**
Case number 11	De novo 2q31.1 deletion (13.9 Mb), pathogenic CNV	Yes

Mosaicism and CF DNA:

- Placental mosaic confined to type 1 placenta:

Risk of **false positive** for the fetus, detection depending on the **fetal fraction**

- Placental mosaic confined to type 2 placenta and mosaic confined to foetus:

Risk of **false negative**

Results 3/3: **100%** of abnormalities **detected** by CF DNA with a poor neurodevelopmental prognosis and normal ultrasound

	Genetic abnormality identified n=11	Would have been seen at the extended CF DNA >7Mb
Case number 1	Trisomy 18	Yes
Case number 2	Trisomy 18	Yes
Case number 3	CVS: 47,XY,+22 AF: Mosaic trisomy 22 (20%) (TFM VI)	Yes
Case number 4	CVS: 45,X Mosaic monosomy X (85%) (TFM VI)	Yes
Case number 5	*Patient seen at 2nd semester* AF: Mosaic trisomy 16 (8%)	No
Case number 6	CVS 47,XY,+16 AF: Mosaic trisomy 16 (10%)	Yes
Case number 7	Confined placental mosaicism for trisomy 2 (50%) (CPM II)	Yes
Case number 8	Confined placental mosaicism for trisomy 13 (5%) (Probably CPM I)	No
Case number 9	4q35.1q35.2 deletion inherited from the father (2.6 Mb), probably benign CNV	No
Case number 10	6q15q16.1 deletion inherited from the father (2.1 Mb), probably benign CNV	No
Case number 11	De novo 2q31.1 deletion (13.9 Mb), pathogenic CNV	Yes

Risking to delay formal diagnosis

What women want to detect?

Strengths and limitations

*A high-risk cohort with **no ultrasound abnormalities**:*

- French guidelines
- A **single centre** for CMA analysis
- Cases assessed by **expert cytogeneticists**
- Ultrasound by **referring physician**
- Examination of all newborn babies by a **paediatrician**
- **89% acceptability rate for IT**

*A unicentric cohort, **non-exhaustive** chromosomal abnormalities:*

- Small cohort
- Only CNV detectable by CMA
- No information on children's mid-term development

→ Need for a **multicentre** study with a **larger sample size**

Conclusion

- Chromosomal abnormalities detected: **rare and heterogeneous**
- **Not all detectable** by high-resolution CF DNA
- **100%** of abnormalities **detected** by CF DNA with a **poor neurodevelopmental prognosis and normal ultrasound** A risk-benefit balance between: source of anxiety and risking to delay formal diagnosis
- **Low PAPP-A** as an indicator of chromosomal abnormality
- Importance of the **pre-test and post-test consultation** and respect of the **woman's choice**

Acknowledgements

- **Dr DAP Matthieu, Pr MALAN Valérie**
- **Pr Yves VILLE, Pr Julien STIRNEMANN, Dr Raphaël BARTIN**
- **Toutes l'équipe de la Maternité de Necker Enfants Malades en particulier l'équipe du diagnostic anténatal**
- **Pr Serge ROMANA et Dr Marie-Paule BEAUJARD du service de médecine génomique des maladies rares de Necker**
- **Pr Jean-Michel DUPONT et le Secteur de cytogénétique de Cochin**
- **Pr Valérie NIVET ANTOINE et le Service de biochimie de Necker**