Prima visita - counseling prenatale: screening delle anomalie cromosomiche, dei disordini ipertensivi, della sindrome metabolica

Enrico Ferrazzi
Daniela Di Martino

Direttore -MANGIAGALLI CENTER
IRCCS CA GRANDA POLICLINICO

University of Milan, School of Medicine,

Amniocentesi e CVS per età

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Invasive diagnostic testing

CVS / Amnio	Post-test risk
T21, 18 & 13	0
Other chromosomal	1 in 10,000
Uncertain results	1 in 100
Fetal loss	1 in 100
Maternal death	Very rare but not 0

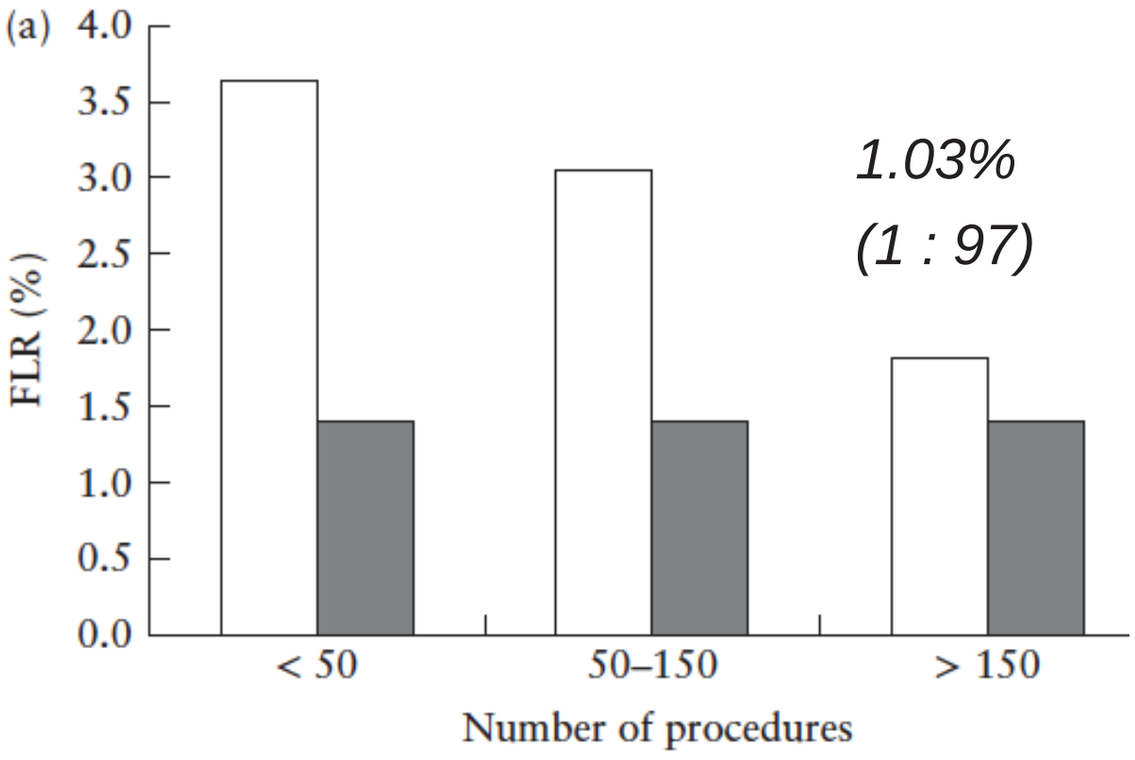
3 feti normali persi per ogni T21

Ultrasound Obstet Gynecol 2017; 49: 599–606
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.15986

Total pregnancy loss after chorionic villus sampling and amniocentesis: a cohort study

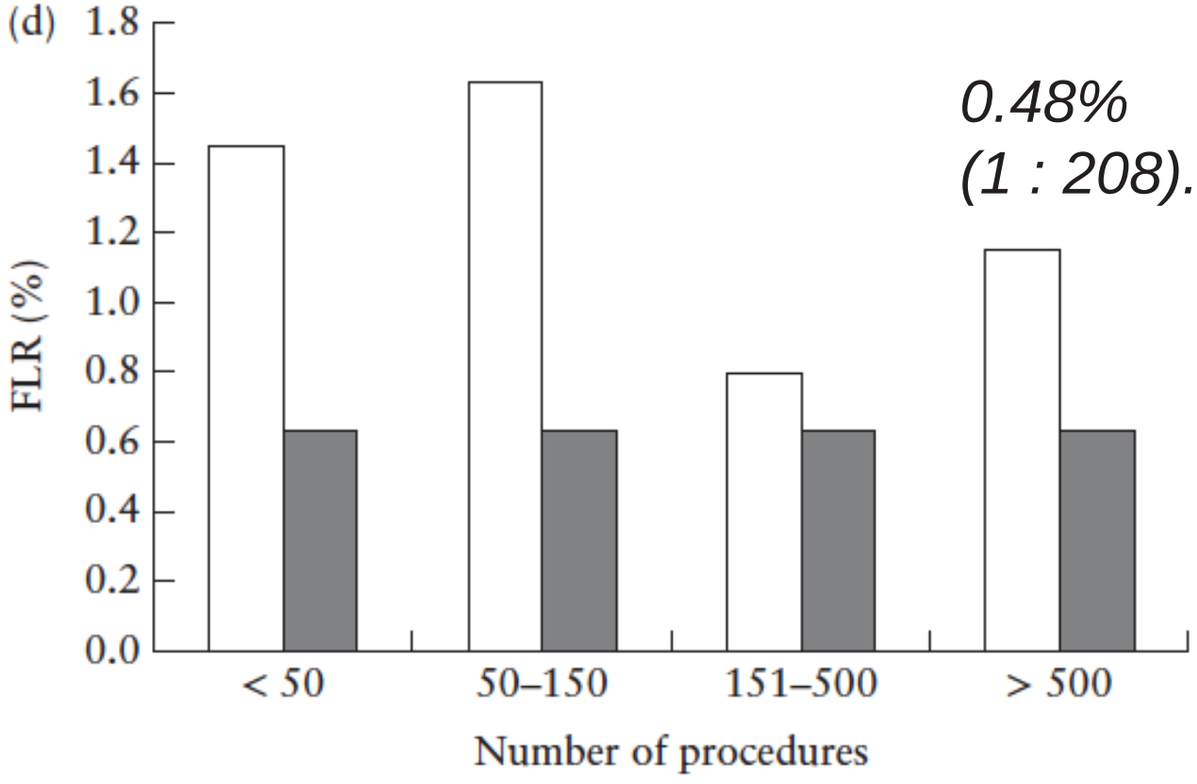
M. BAKKER[1], E. BIRNIE[1,2], P. ROBLES DE MEDINA[3], K. M. SOLLIE[1], E. PAJKRT[3] and C. M. BILARDO[1]

CVS



1.03%
(1 : 97)

amniocentesis



0.48%
(1 : 208).

2018 QUALE SCENARIO

American Journal of Obstetrics and Gynecology (2005) 192, 1761–7

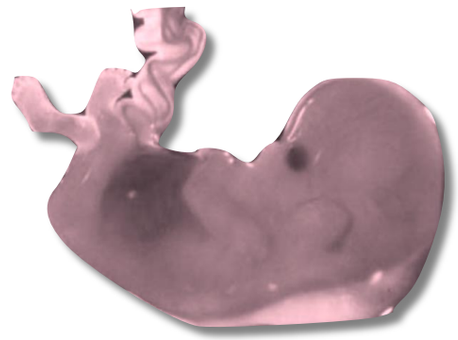
ELSEVIER

American Journal of OBSTETRICS and GYNECOLOGY
www.ajog.org

EDITORS' CHOICE

Prospective first-trimester screening for trisomy 21 in 30,564 pregnancies

Kyriaki Avgidou, MD,[a] Aris Papageorghiou, MD,[a] Renu Bindra, MD,[a] Kevin Spencer, MD,[b] Kypros H. Nicolaides, MD[a,*]



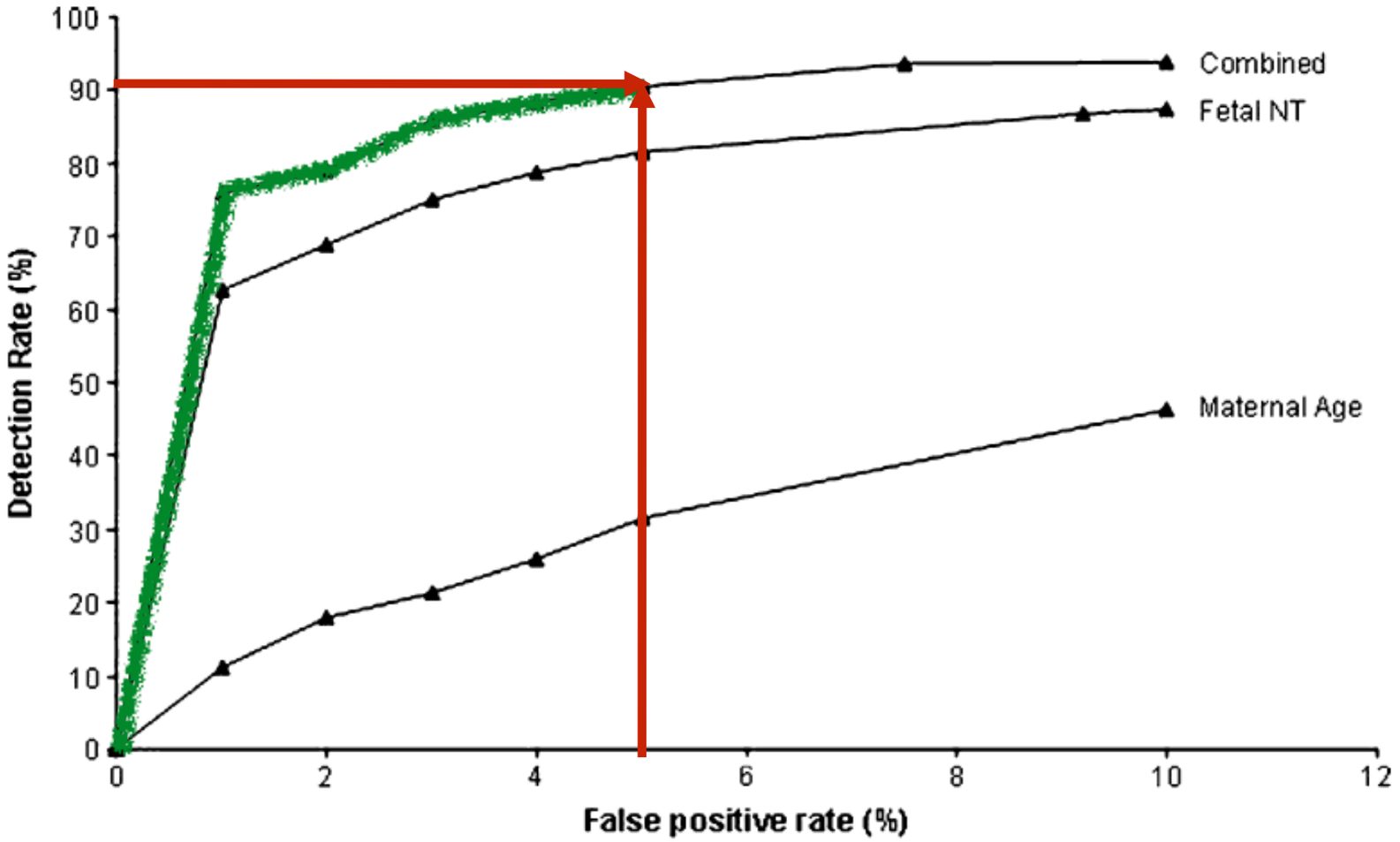


Figure 2 Relationship between detection rates and false-positive rates in screening for trisomy 21 by maternal age alone, maternal age and fetal NT, and by the combination of maternal age, fetal NT, and maternal serum biochemistry.

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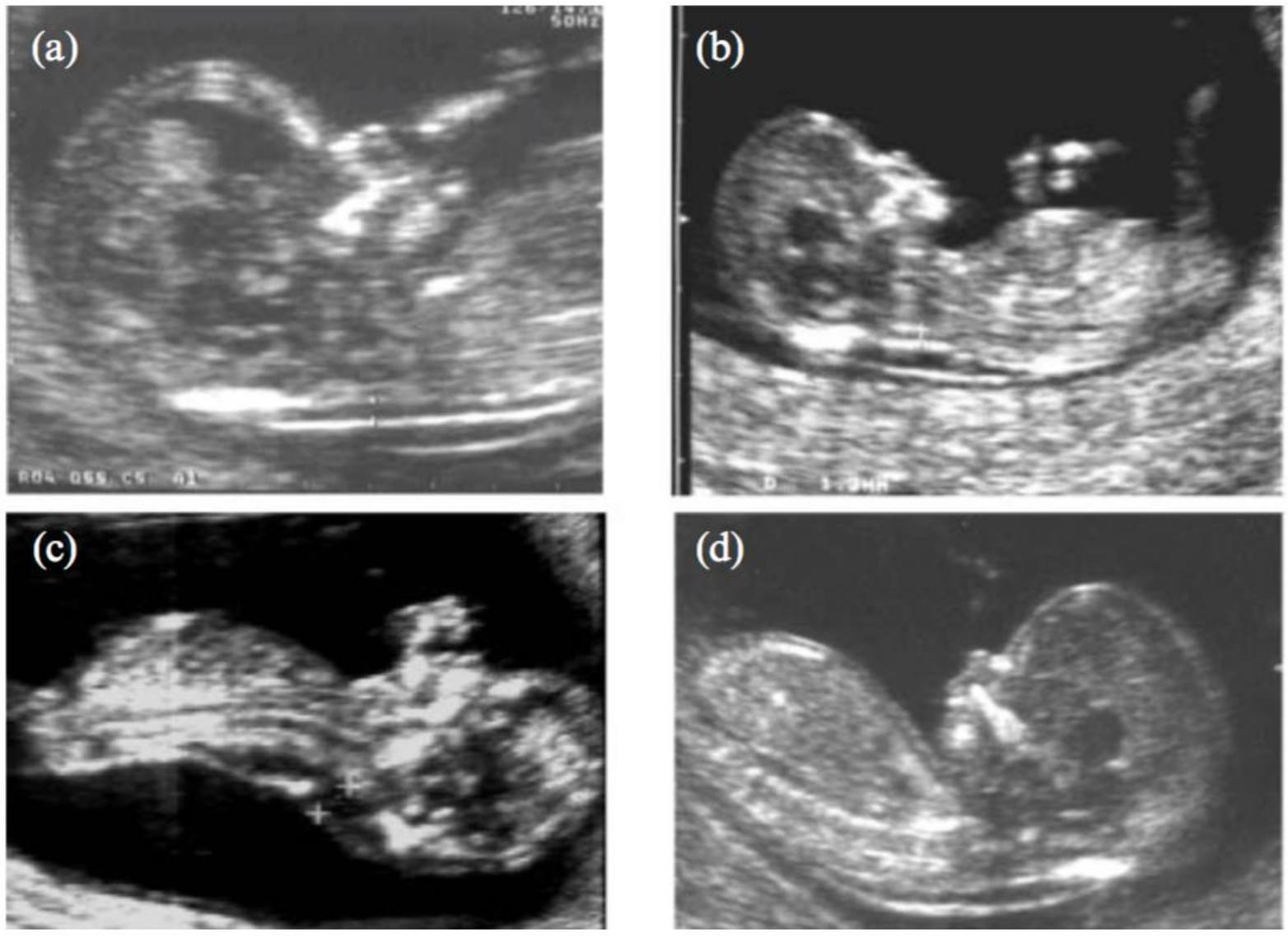

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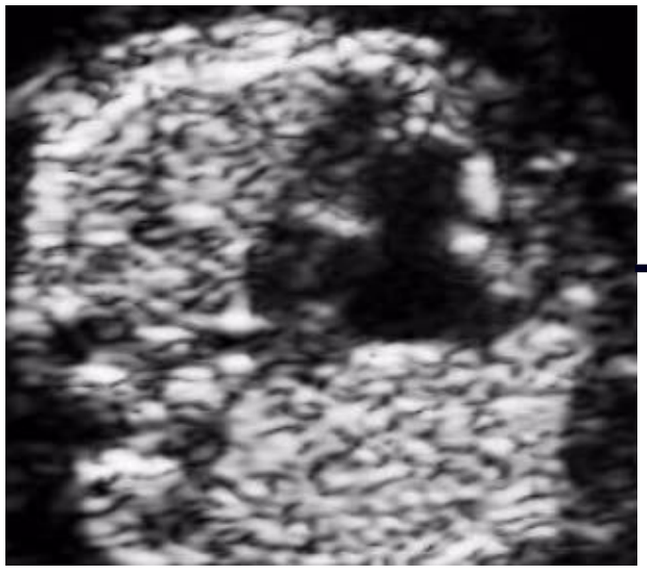
OSPEDALE MAGGIORE POLICLINICO

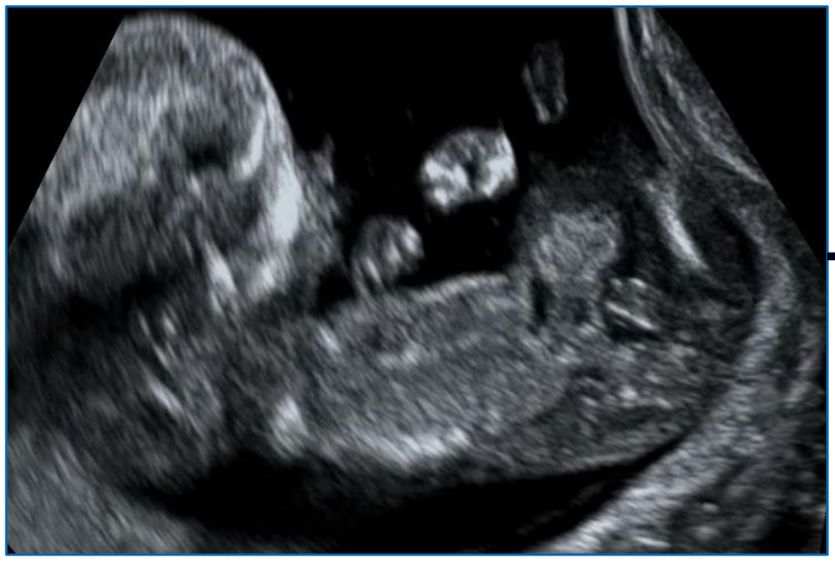
Early detection of fetal defects

Atrioventricular septal defect



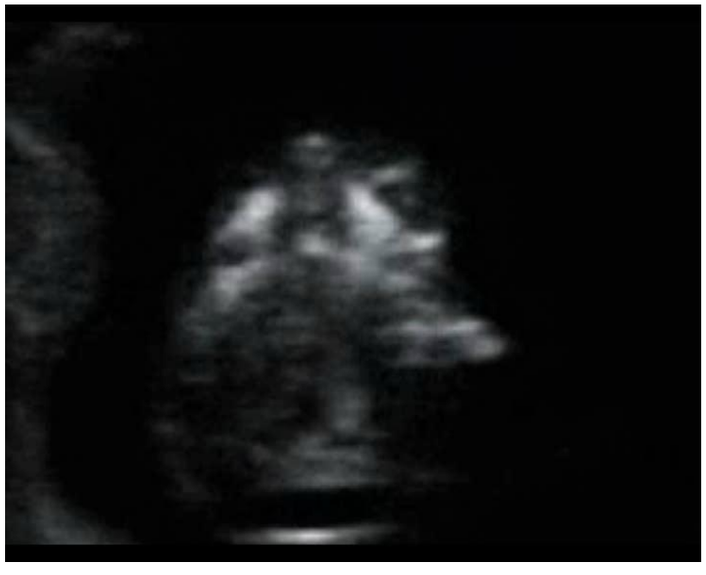
T 21/18/13 = 65%

Exomphalos



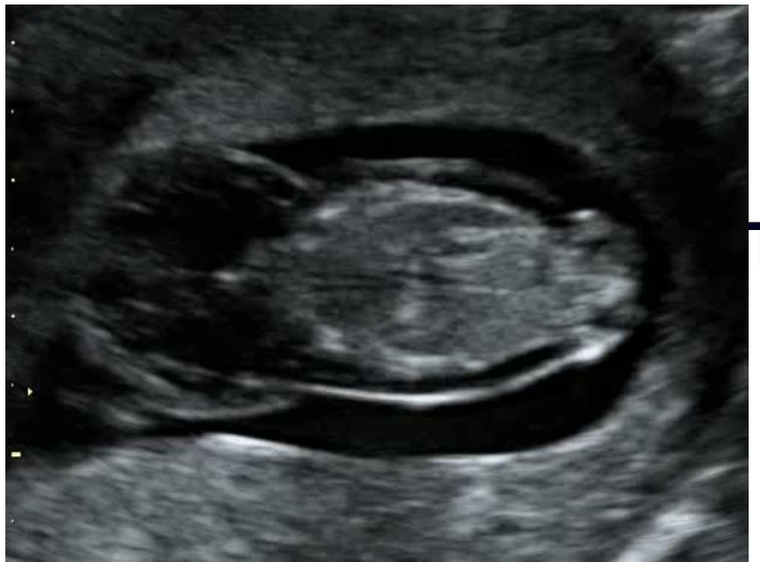
T 18/13 = 55%

Facial cleft



T 18/13 = 83%

Hydrops



T 21/18/13 = 80%

Ultrasound Obstet Gynecol 2016; 47: 45–52
Published online 26 October 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.15783

Clinical implementation of routine screening for fetal trisomies in the UK NHS: cell-free DNA test contingent on results from first-trimester combined test

M. M. GIL*, R. REVELLO*, L. C. POON*, R. AKOLEKAR*† and K. H. NICOLAIDES*

Table 3 Distribution of risk from the combined test according to trisomic outcome

Risk cut-off		*Trisomy 21 (n = 47)*
≥ 1 in 10		30 (63.8)
≥ 1 in 20		36 (76.6)
≥ 1 in 50		38 (80.9)
≥ 1 in 100	+5	41 (87.2)
≥ 1 in 500		46 (97.9)
≥ 1 in 1000		46 (97.9)
≥ 1 in 1500		46 (97.9)
≥ 1 in 2000		46 (97.9)
≥ 1 in 2500	+1	46 (97.9)
≥ 1 in 3000		46 (97.9)
≥ 1 in 3500		47 (100)

11.692

The combined test
detection rate of 87% for T21
detection rate of 93% for T18/13
a FPR of 3.4%;

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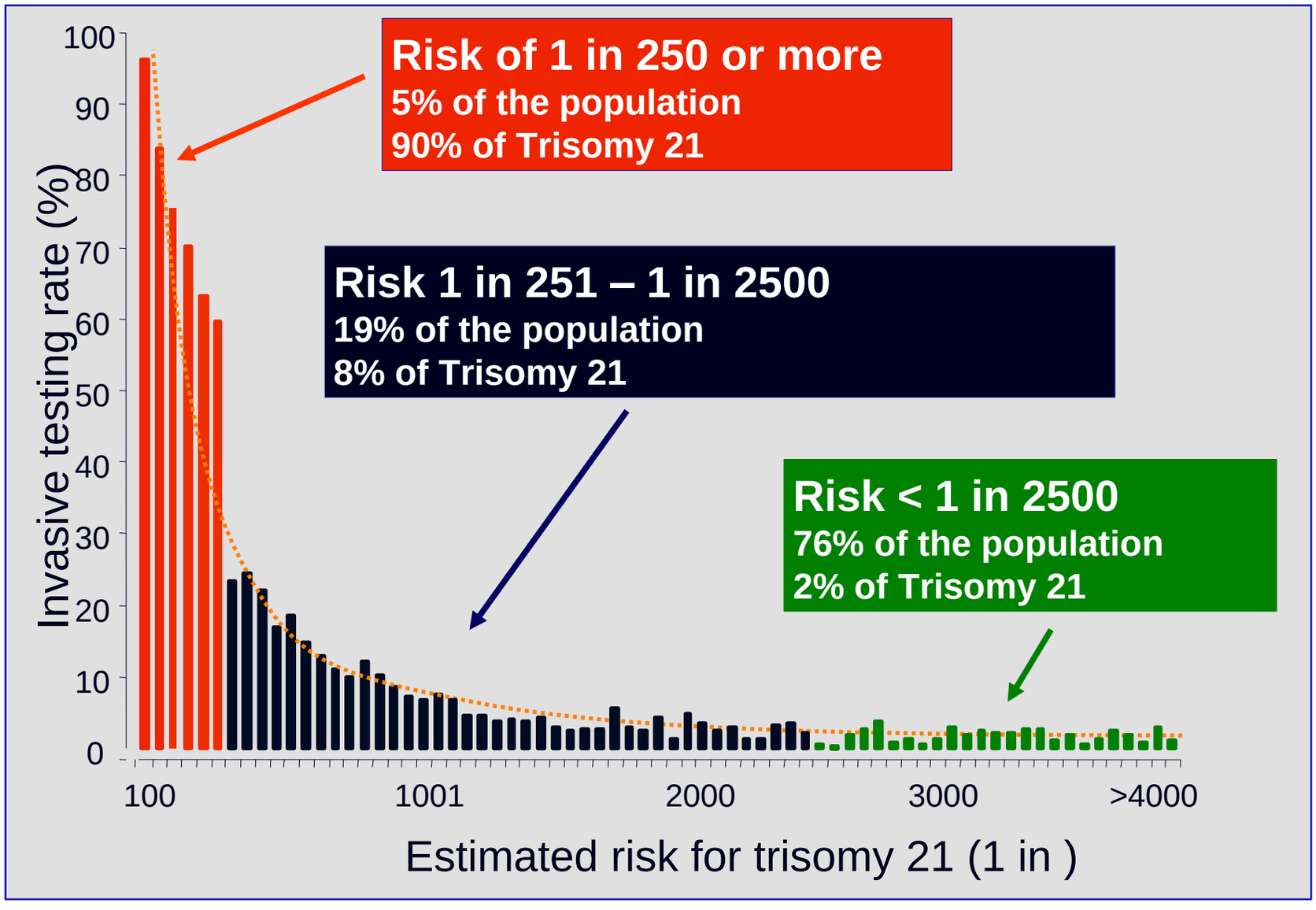
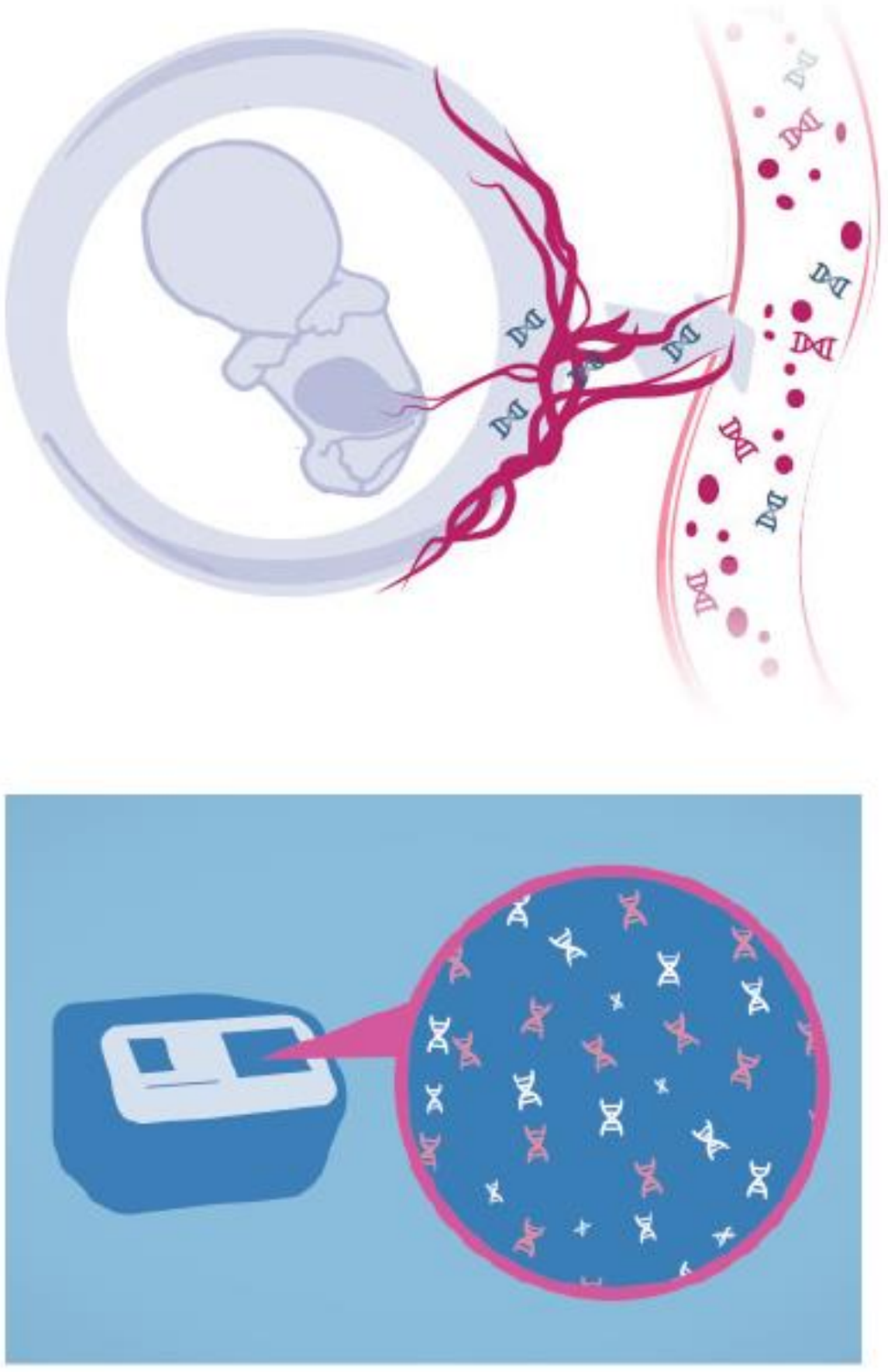
OSPEDALE MAGGIORE POLICLINICO

Risk distribution





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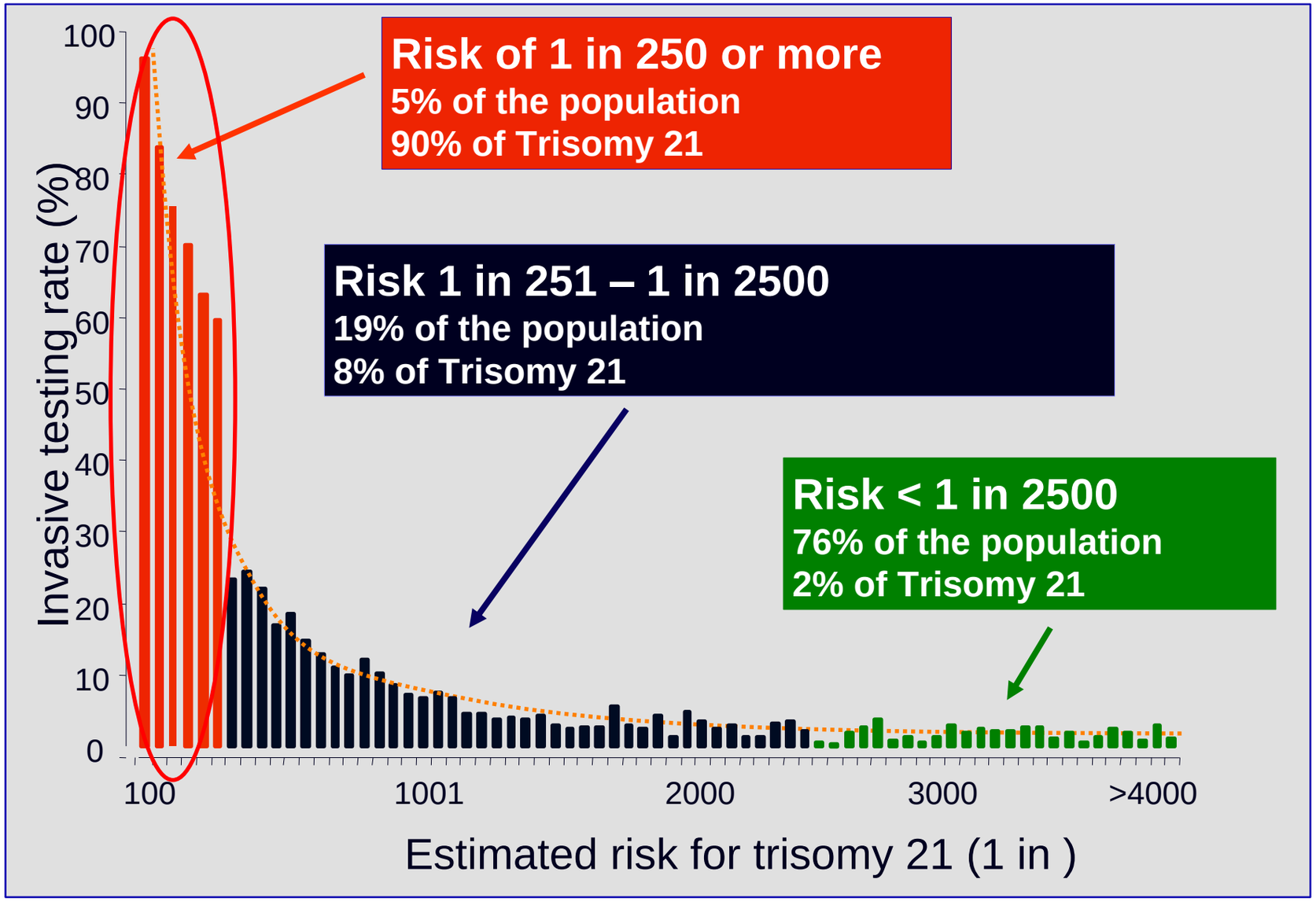
Risk distribution

Contingent screening



Risk ≥ 1 in ?

- **cfDNA to all?**
- **Risk stratification?**
- **Nuchal translucency?**
- **Major fetal defects?**

Impact on invasive testing rate

Ultrasound Obstet Gynecol 2016; 47: 45–52
Published online 26 October 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.15783

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≥ 1 in 1500	46 (97.9)
≥ 1 in 2000	46 (97.9)
≥ 1 in 2500	46 (97.9)
≥ 1 in 3000	46 (97.9)
≥ 1 in 3500	47 (100)

Women with a risk **≥1 in 100 (high-risk group) were offered options of invasive testing,** cfDNA testing or no further testing,

Women with a between **1 in 101 and 1 in 2500 (intermediate-risk group) were offered cfDNA testing or no further testing**

Ultrasound Obstet Gynecol 2016; 47: 45–52
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Clinical implementation of routine screening for fetal trisomies in the UK NHS: cell-free DNA test contingent on results from first-trimester combined test

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≥ 1 in 3000		46 (97.9)
≥ 1 in 3500		47 (100)

The combined test
detection rate of 87% for T21
detection rate of 93% for T18/13
a FPR of 3.4%;

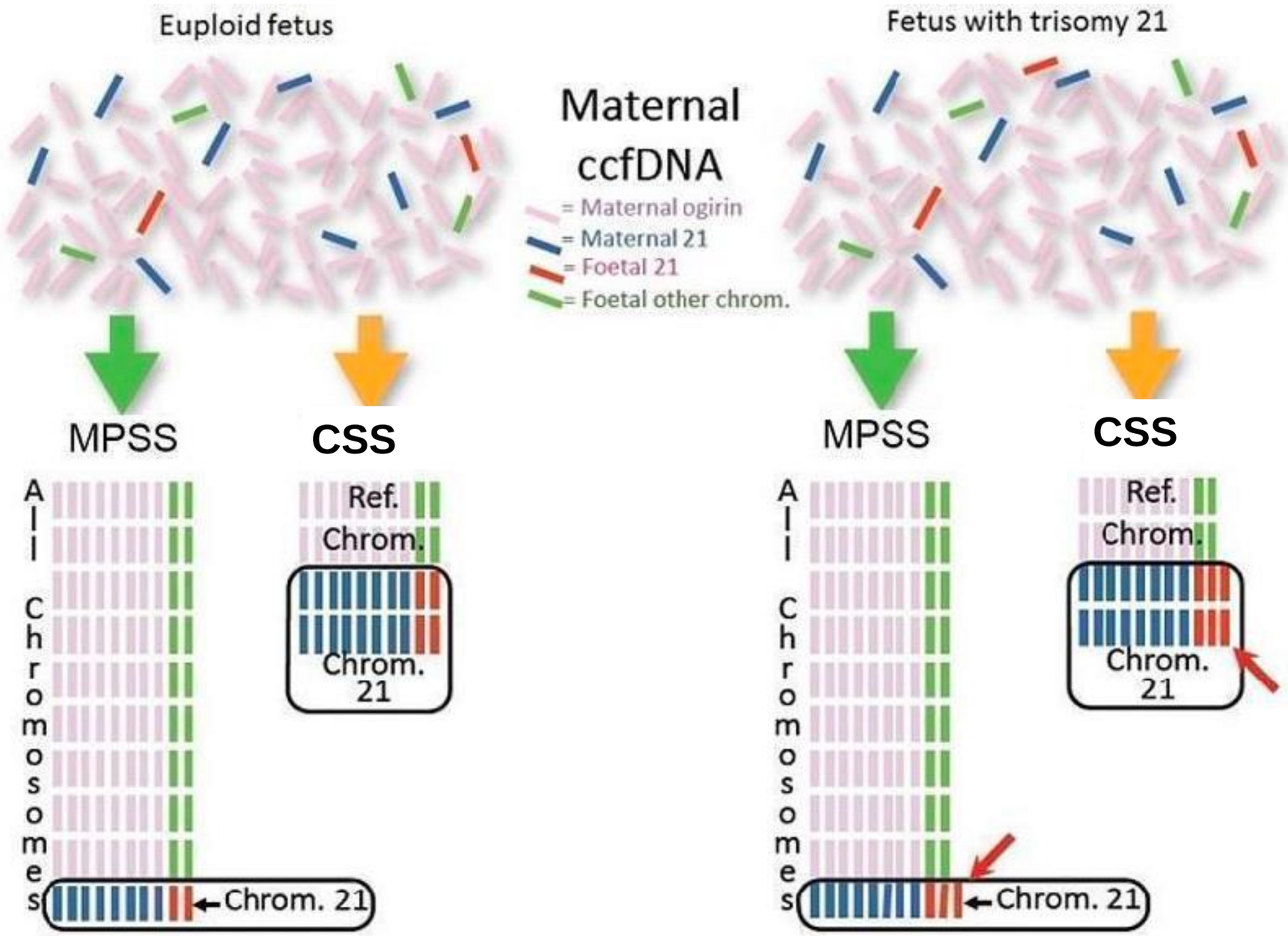
cfDNA test
detection rate of 98% for T21
detection rate of 82% for T18/13 a FPR of 0.25%.

Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women (Protocol)

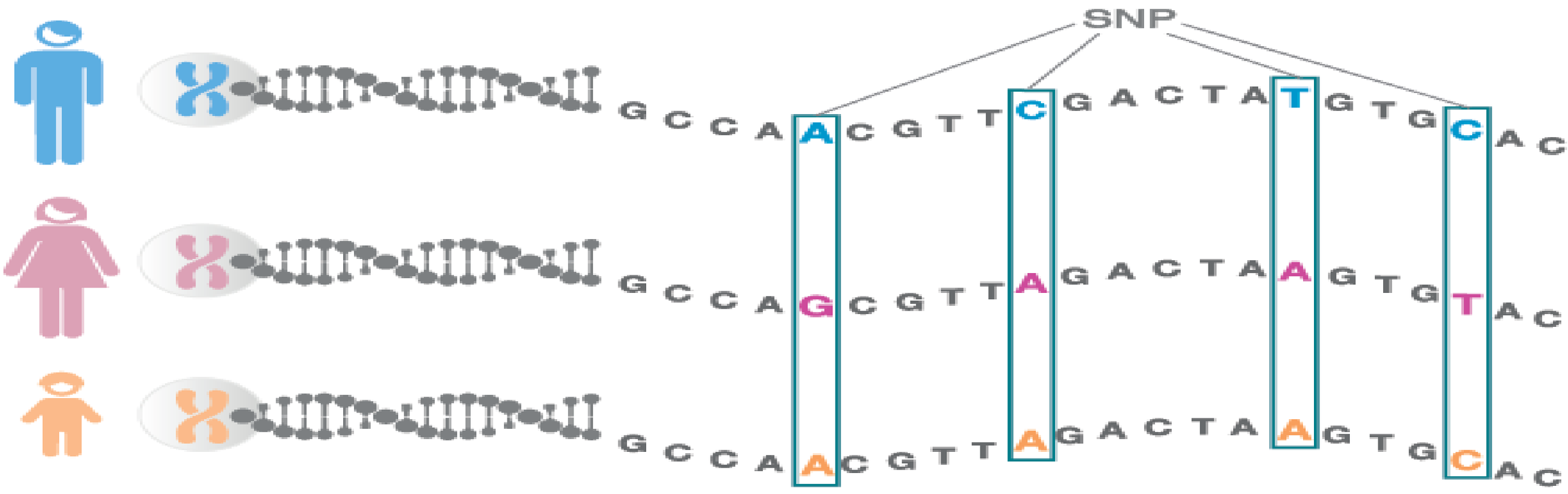
Badeau M, Lindsay C, Blais J, Takwoingi Y, Langlois S, Légaré F, Giguère Y, Turgeon AF, Witteman W, Rousseau F

Cochrane Library

Cochrane Database of Systematic Reviews



SNP = Single Nucleotide Polymorphism



- Polymorphisms occur when a single base pair (nucleotide) is changed: A, T, C, or G
- These are **normal** genetic changes that occur in every person and mark where people differ from one another

metanalisi delle casistiche pubblicate con le tre metodologie:

1. CSS, chromosome- specific sequencing
2. MPSS, massively parallel shotgun sequencing
3. SNP, single nucleotide polymorphism

Ultrasound Obstet Gynecol 2017; **50**: 302–314
Published online 27 July 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17484

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

M. M. GIL[1,2,3], V. ACCURTI[1], B. SANTACRUZ[2], M. N. PLANA[4] and K. H. NICOLAIDES[1]

[1]*Fetal Medicine Research Institute, King's College Hospital, London, UK;* [2]*Obstetrics and Gynecology Department, Torrejon University Hospital, Torrejon de Ardoz, Madrid, Spain;* [3]*Obstetrics and Gynecology Department, Universidad Francisco de Vitoria, Pozuelo de Alarcón, Madrid, Spain;* [4]*Clinical Biostatistics Unit, Ramón y Cajal Hospital (IRYCIS), CIBER Epidemiology and Public Health (CIBERESP), Madrid, Spain*

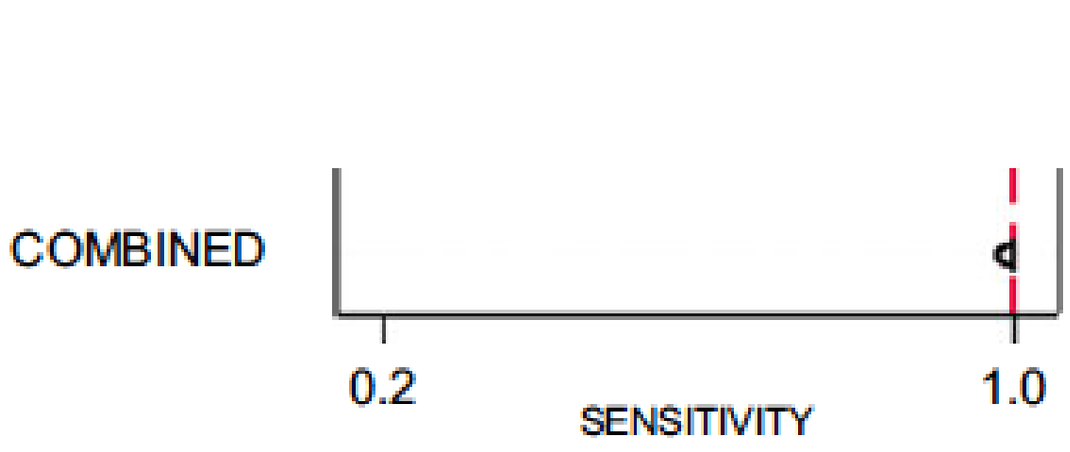
Quezada (2015)[26]	CSS	10 (10–11)	T21,T18,T13	53/2905 (1.8)
Gil (2016)[30]	CSS	12 (11–13)	T21	1/54 (1.9)
Mnyani (2016)[33]	SNP	14 (13–21)	T13	2/82 (2.4)
Qi (2016)[38]	MPSS	19 (11–30)	T21,T18,T13	4/2828 (0.1)
Ma (2017)[40]	MPSS	19 (—)	T21,T18,T13	15/10 594 (0.1)

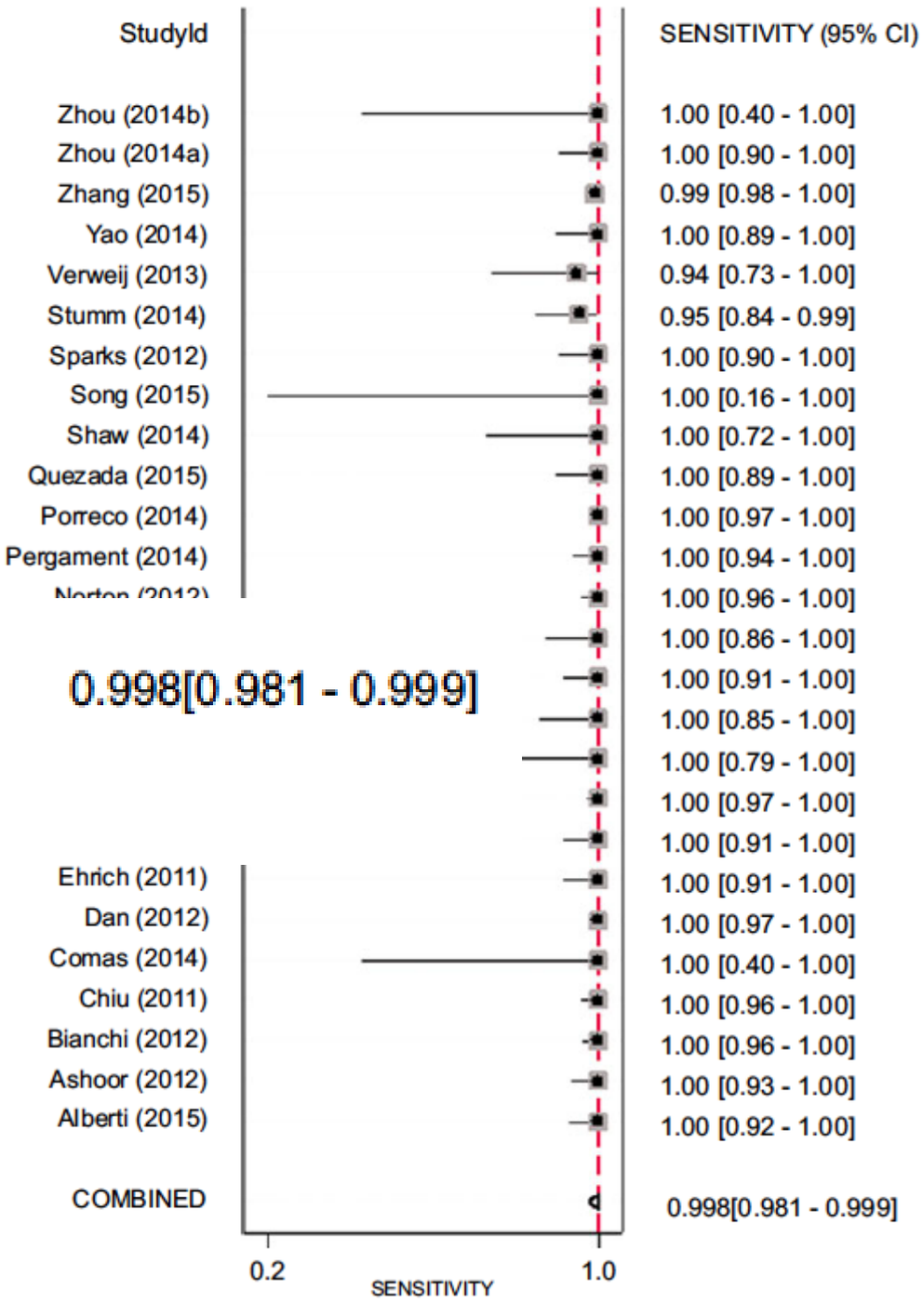
AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS SYSTEMATIC REVIEW

Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population – a systematic review and meta-analysis

ERIK IWARSSON[1,*], BO JACOBSSON[2,3,*], JESSICA DAGERHAMN[4], THOMAS DAVIDSON[4,5], EDUARDO BERNABÉ[6] & MARIANNE HEIBERT ARNLIND[4,7]





Ultrasound Obstet Gynecol 2015; 45: 249–266
Published online 1 February 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.14791

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*†

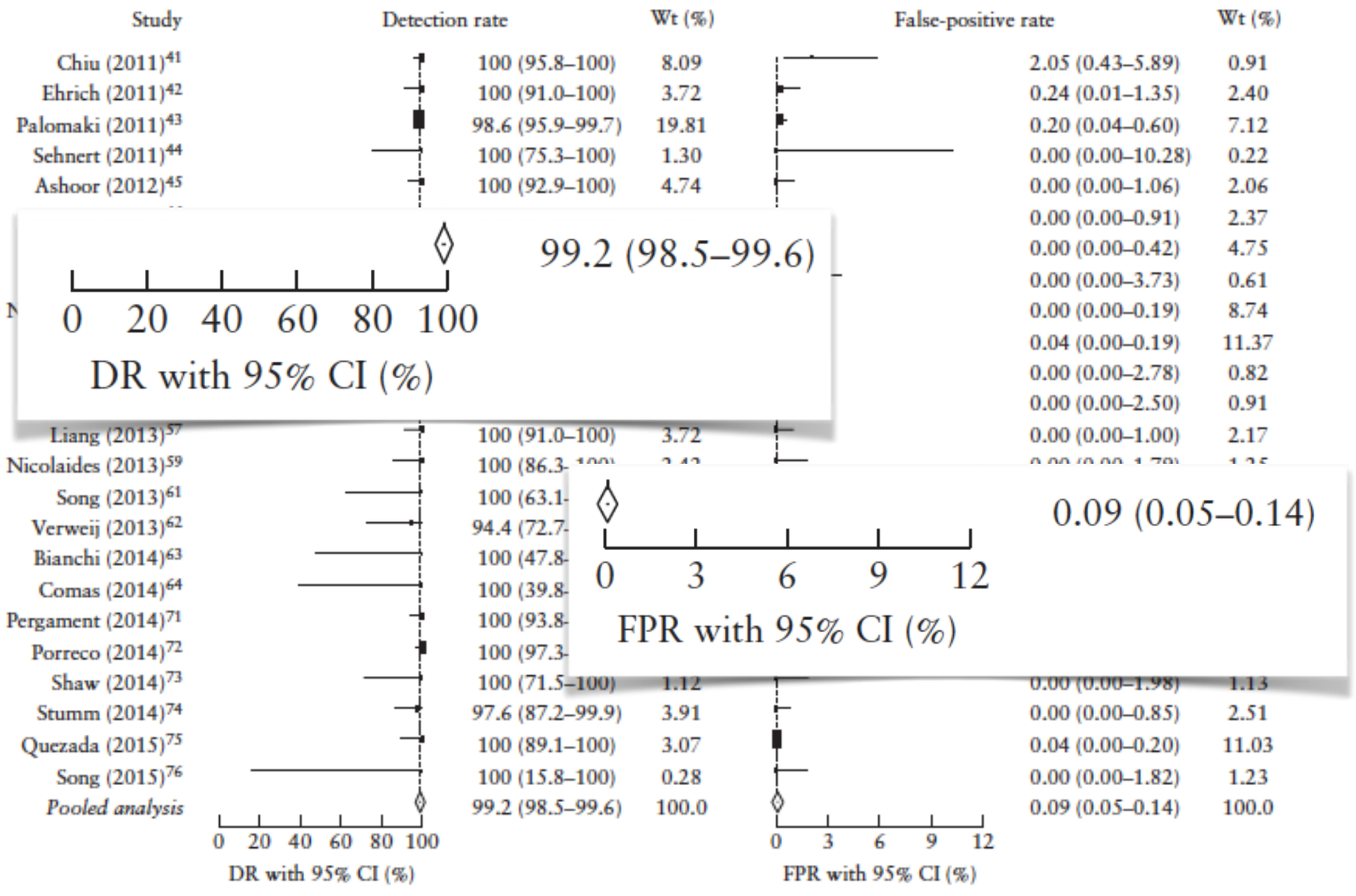


Figure 4 Forest plots of detection rates (DR) and false-positive rates (FPR) with 95% CIs and weighted pooled summary statistics using the random-effects model in assessing cell-free DNA analysis in screening for trisomy 21 in singleton pregnancy. Only the first author of each study is given.

DOI: 10.1002/pd.4773

ORIGINAL ARTICLE

Cell-free DNA testing in the maternal blood in high-risk pregnancies after first-trimester combined screening

Nicola Persico[1]*, Simona Boito[1], Benedetta Ischia[1], Adalgisa Cordisco[2], Valentina De Robertis[3], Isabella Fabietti[1], Enrico Periti[2], Paolo Volpe[3], Luigi Fedele[1] and Georgios Rembouskos[3]

259 singleton pregnancies

estimated risk for trisomies 21, 18 or 13 ≥1 in 250

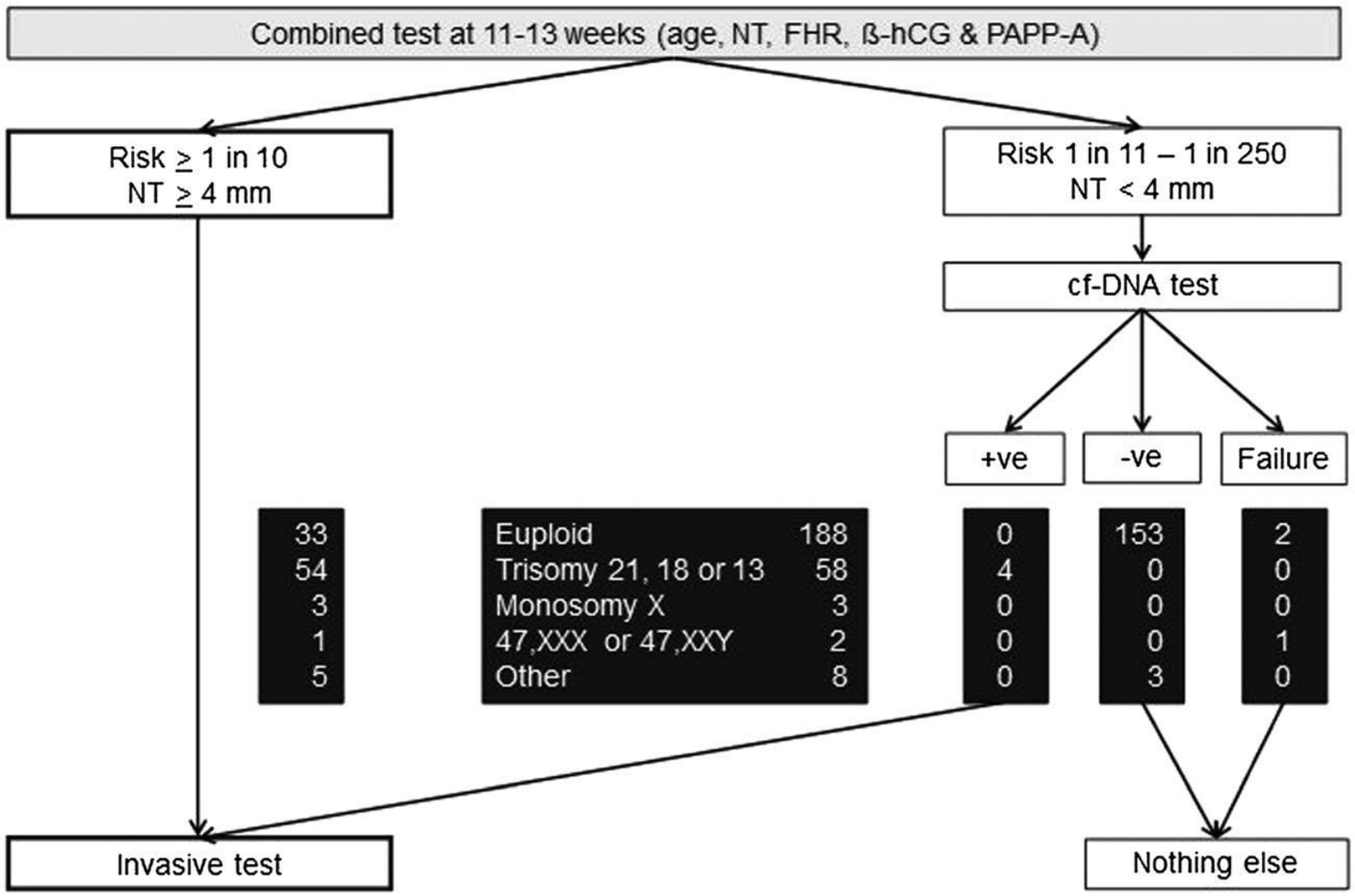


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Table 1 **Results from cfDNA testing according to fetal karyotype**

		Cell free DNA test			
Fetal karyotype	*n*	No result	Result	Screen +ve	Screen -ve
Euploid	188	4 (2.1)	184	—	184 (100)
Trisomy 21	37	1 (2.7)	36	35 (97.2)	1 (2.8)
Trisomy 18	15	2 (13.3)	13	13 (100)	—
Trisomy 13	6	1 (16.7)	5	5 (100)	—
Monosomy X	3	0 (0.0)	3	2 (66.7)	1 (33.3)
47,XXX or 47, XXY	2	1 (50.0)	1	1 (100)	—
Other	8	1 (12.5)	7	—	7 (100)
Total	259	10 (3.9)	249	56 (22.5)	193 (77.5)

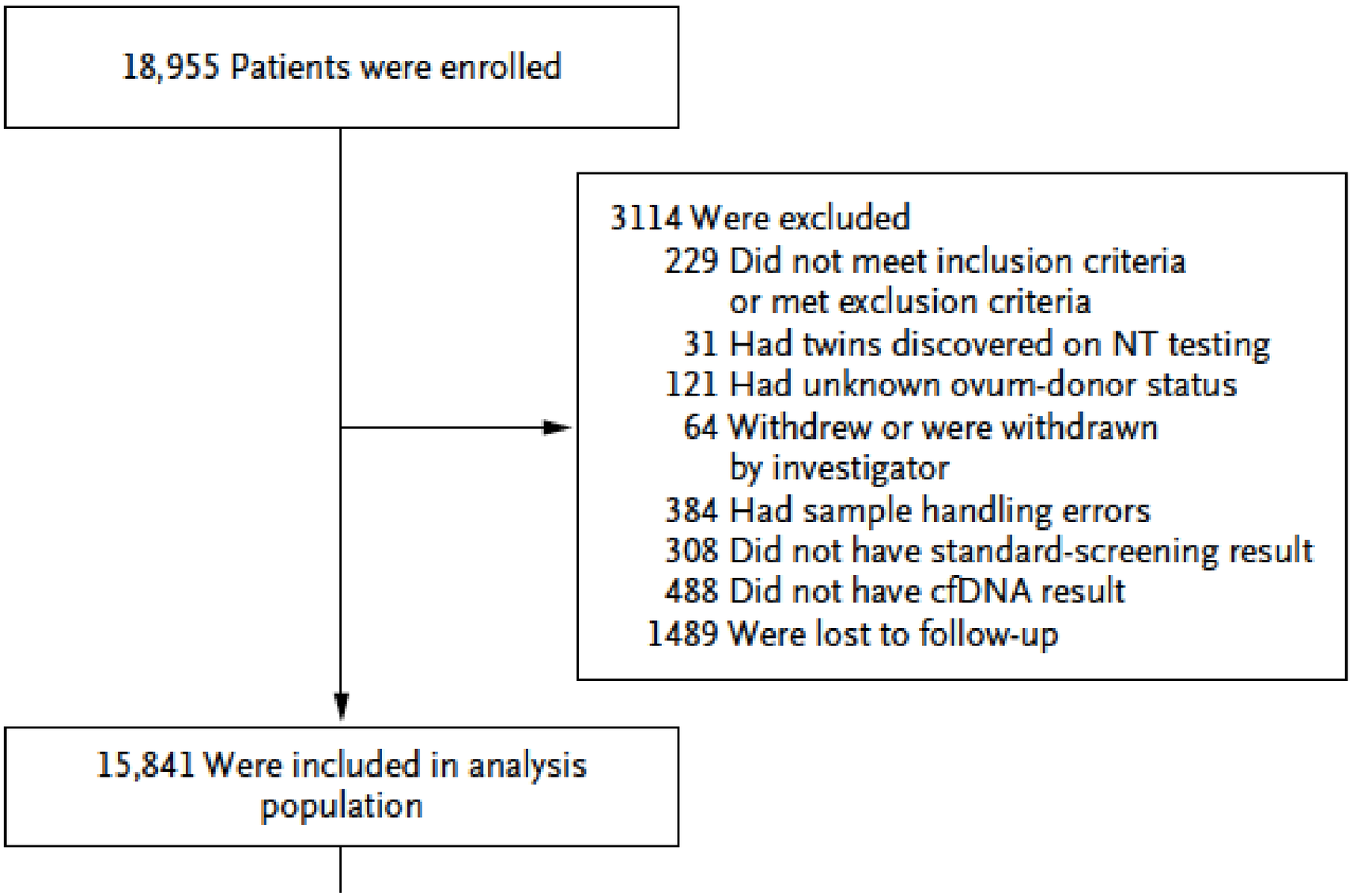
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 23, 2015 VOL. 372 NO. 17

Cell-free DNA Analysis for Noninvasive Examination of Trisomy

Mary E. Norton, M.D., Bo Jacobsson, M.D., Ph.D., Geeta K. Swamy, M.D., Louise C. Laurent, M.D., Ph.D., Angela C. Ranzini, M.D., Herb Brar, M.D., Mark W. Tomlinson, M.D., Leonardo Pereira, M.D., M.C.R., Jean L. Spitz, M.P.H., Desiree Hollemon, M.S.N., M.P.H., Howard Cuckle, D.Phil., M.B.A., Thomas J. Musci, M.D., and Ronald J. Wapner, M.D.

CSS, chromosome- specific sequencing



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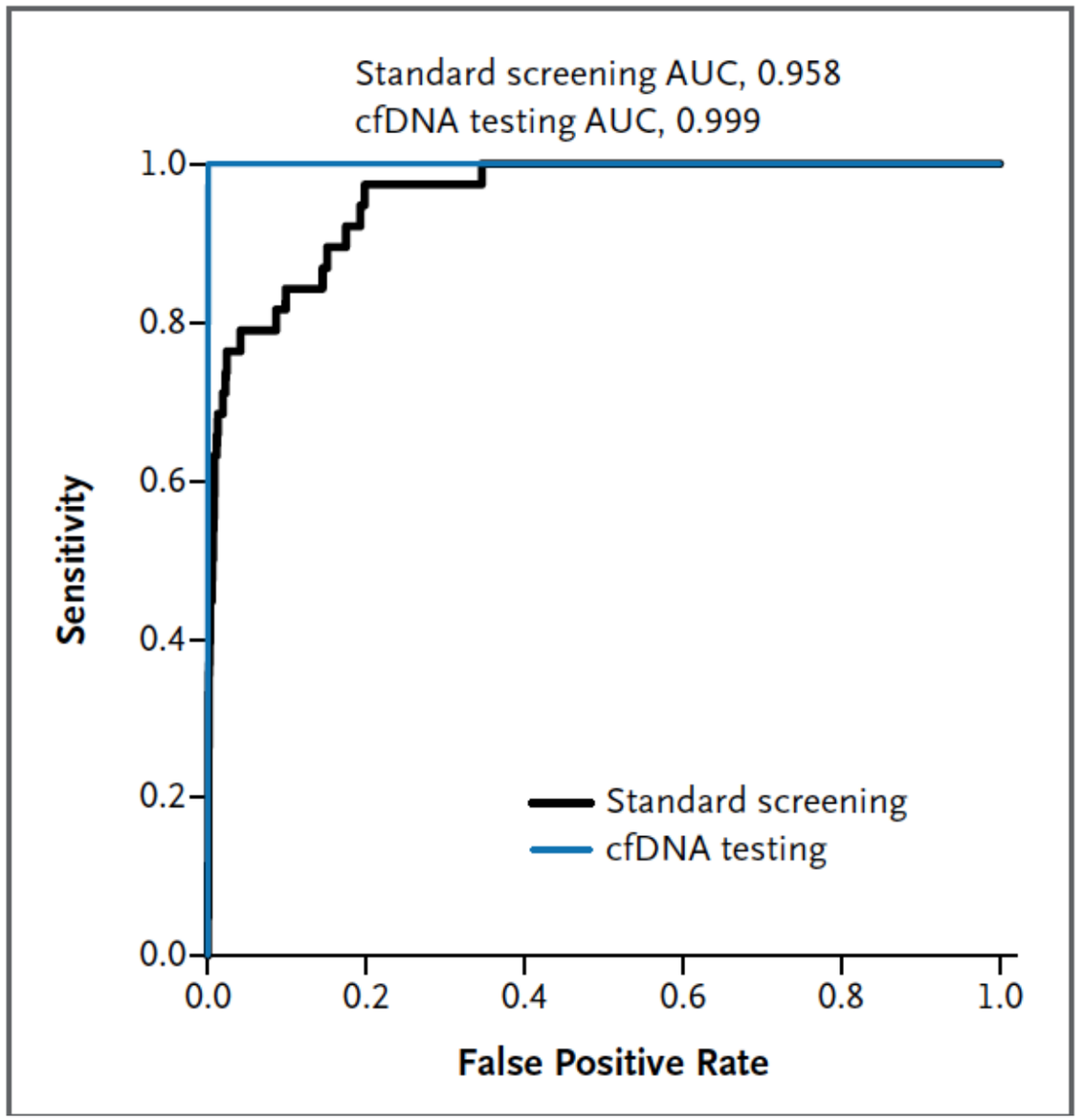
CSS, chromosome- specific sequencing

Trisomy 21 =

CSS: 38 of 38 women (100%; 95%CI, 90.7 to 100)

Standard: 30 of 38 women (78.9%; 95%CI, 62.7 to 90.4)

False positive rates
CSS 0.06%
Standard 5.4%



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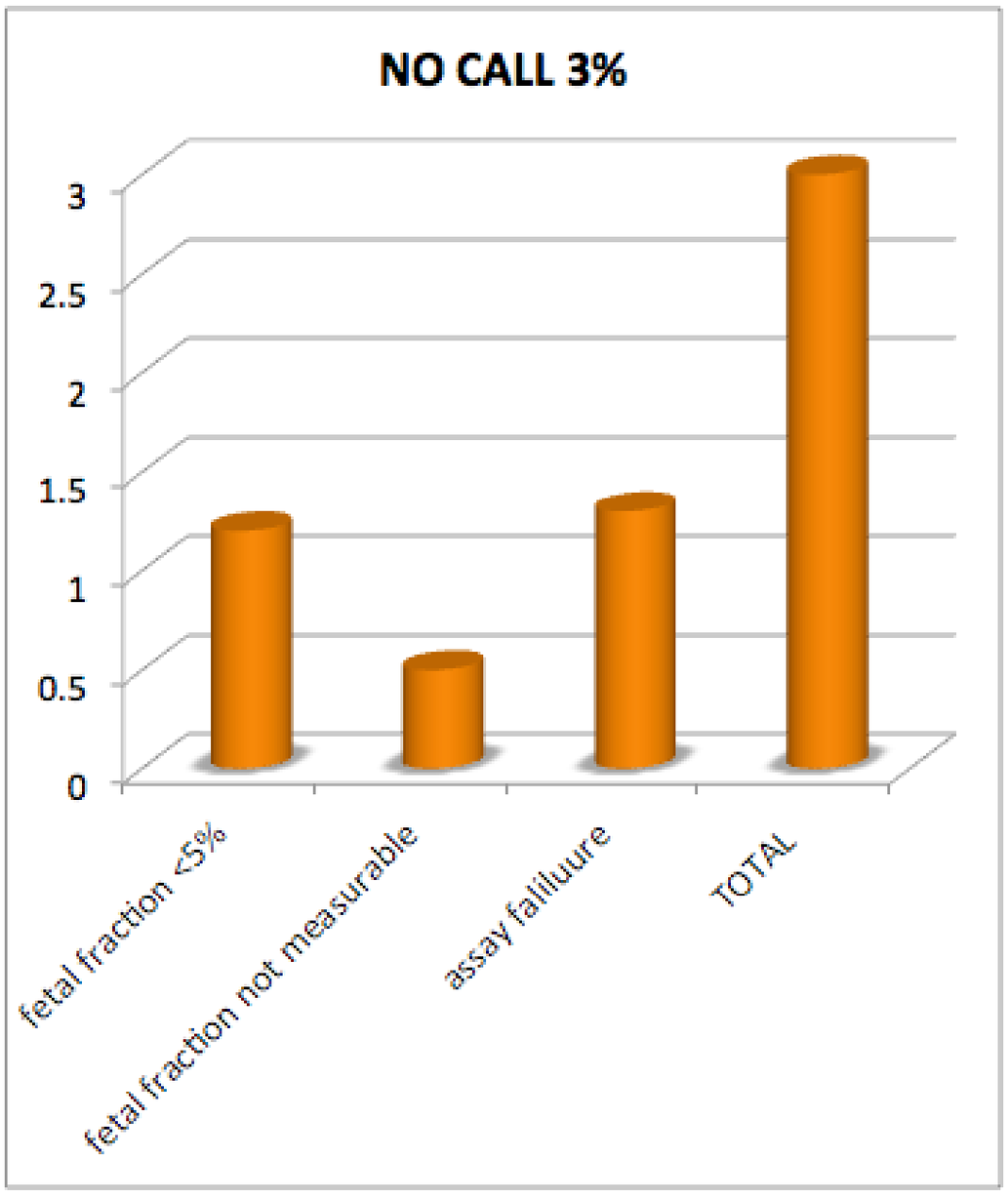


CSS, chromosome- specific sequencing

In the group with no results on cfDNA testing,
there were:
3 trisomy 21,
1 trisomy 18,
2 trisomy 13,
4 triploidy,
1 trisomy 16 mosaic,
1 deletion 11p,
1 w structurally abnormal chromosome

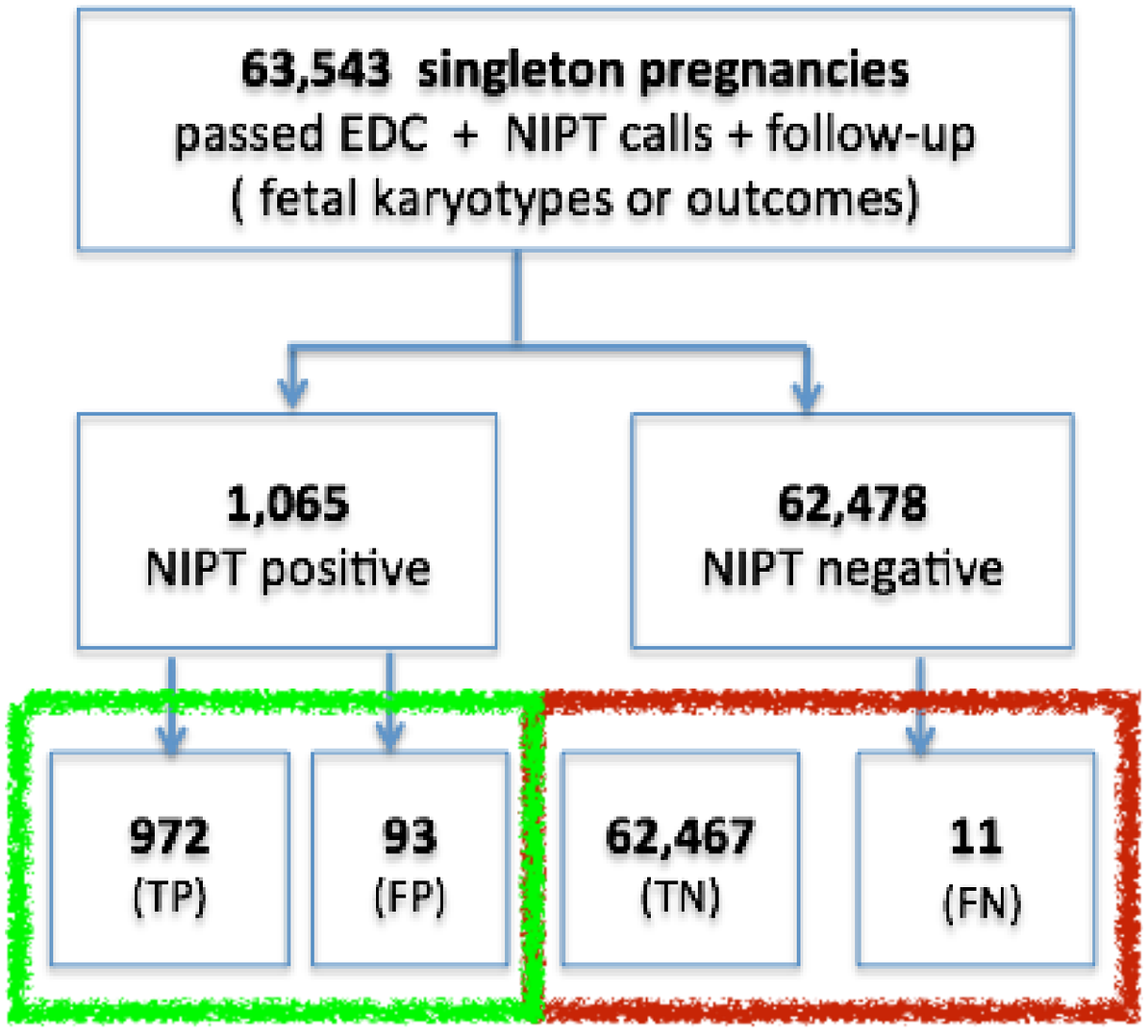
The prevalence of aneuploidy in this group 2.7%

The prevalence of aneuploidy in in the overall cohort
0.4%

massive parallel genome sequencing | performance for aneuploidy

178,719 NIPT tests by Aug 2013

- Resampling/retesting: 2.8%;
- No call rate: 0.069%;



T21	
Specificity	99.95%
Sensitivity	99.22%
PPV	95.73%
NPV	99.99%
T18	
Specificity	99.95%
Sensitivity	97.34%
PPV	84.72%
NPV	99.99%
T13	**with 95% CI**
Specificity	99.96% (99.95-99.97%)
Sensitivity	100.00% (87.2-100%)
PPV	51.92% (38.3-65.5%)
NPV	100.00% (99.99-100%)

Linee guida

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

Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 640, September 2015 *(This Committee Opinion Replaces Committee Opinion Number 545)*

Committee on Genetics
Society for Maternal-Fetal Medicine

Recommendations

- Cell-free DNA screening does not assess risk of fetal anomalies . Patients who are undergoing cell-free DNA screening should be offered ultrasound evaluation for risk assessment.

  Women whose results are not reported, indeterminate, or uninterpretable (a "no call" test result) from cell-free DNA screening should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy.

  a diagnostic test should be recommended for a patient who has a positive cell-free DNA test result.

-

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

Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 640, September 2015 *(This Committee Opinion Replaces Committee Opinion Number 545)*

Committee on Genetics
Society for Maternal-Fetal Medicine

Recommendations

- A discussion of the risks, benefits, and alternatives …should occur with all patients.
- Given the performance of conventional screening methods, the limitations of cell-free DNA screening performance, and the limited data on cost-effectiveness in the low-risk obstetric population, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population.
- Although any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status, the patient choosing this testing should understand the limitations and benefits of this screening paradigm…
- The cell-free DNA test will screen for only the common trisomies and, if requested, sex chromosome composition.
-

Royal College of Obstetricians & Gynaecologists

Non-invasive Prenatal Testing for Chromosomal Abnormality using Maternal Plasma DNA

In April 2013, the **International Society for Prenatal Diagnosis** published a position statement which concluded that maternal plasma DNA testing may be considered **in women classified as high-risk…**
by previous screens or assessed as high-risk maternal age, the presence of an ultrasound finding suggestive of trisomy 21, 18 or 13,

Royal College of Obstetricians & Gynaecologists

Non-invasive Prenatal Testing for Chromosomal Abnormality using Maternal Plasma DNA

7.2.1 Contingent (step-wise) screening

The use of maternal plasma MPS within a contingent approach would mean continuing combined testing and then to offer the maternal plasma DNA test to the subgroup (perhaps 20%) identified as higher risk.

The cut-off to offer maternal plasma MPS could be set to manage the numbers and resulting costs and this approach could significantly reduce the invasive procedure numbers (by greatly reducing the false-positive rate).

Possible sources of error

5.1 Early gestational age

5.2 Maternal obesity

5.3 Multiple pregnancies

monochorionic (and so monozygotic), both fetuses will be affected or unaffected. Since the amount of cffDNA is approximately double that of a singleton pregnancy,51 cffDNA aneuploidy testing will not only be possible but probably more effective than in singletons.
dichorionic, and so may be discordant, maternal plasma DNA testing would, in theory, not be as straightforward. The complexity introduced by twin pregnancies suggests that, prior to cffDNA testing, a good quality ultrasound scan would be a valuable first step in all pregnancies, to detect empty pregnancy sacs, for example, with fetal medicine counselling when one is suspected.

5.4 Placental mosaicism.

approximately 1% of CVS samples, a phenomenon often called ‘confined placental mosaicism’.

5.5 Maternal conditions

Maternal chromosomal abnormalities, including mosaicism or malignant disease, could be very rare causes of discordant results.

Effects of Maternal and Fetal Characteristics on Cell-Free Fetal DNA Fraction in Maternal Plasma

Reproductive Sciences
1-7

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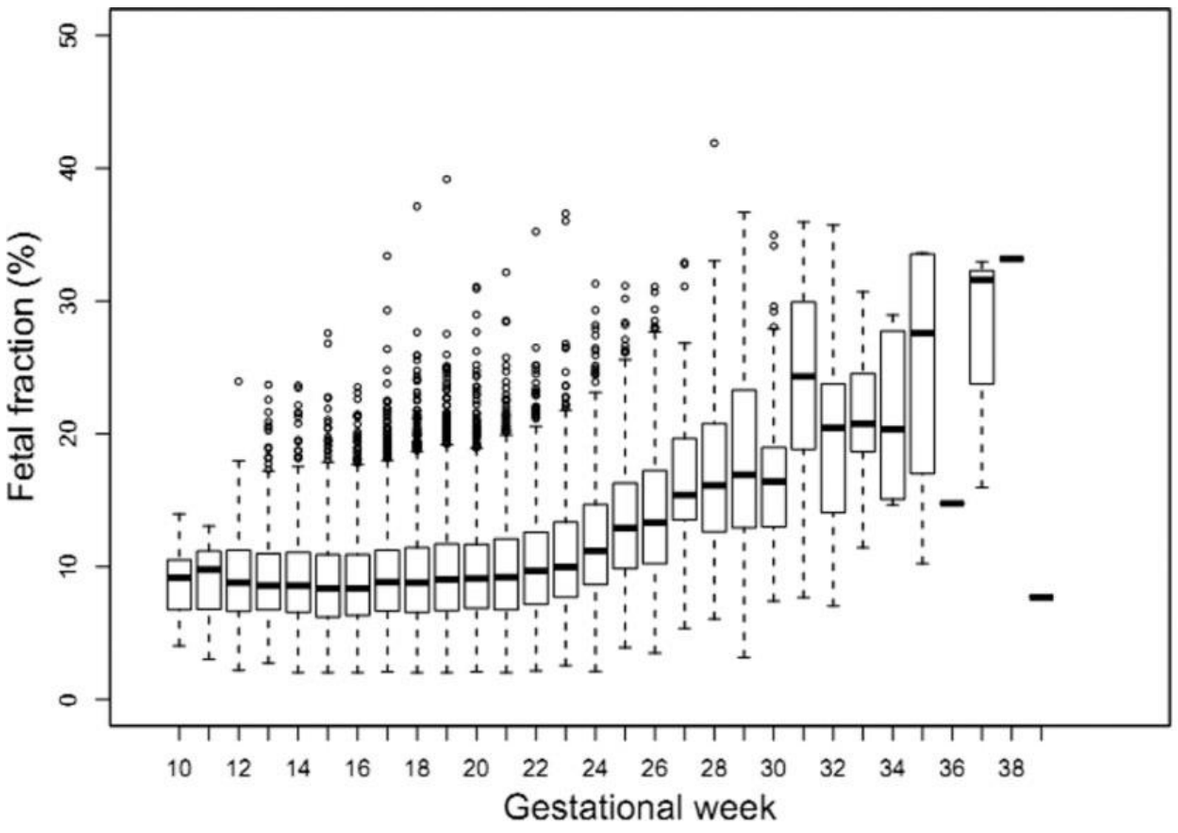

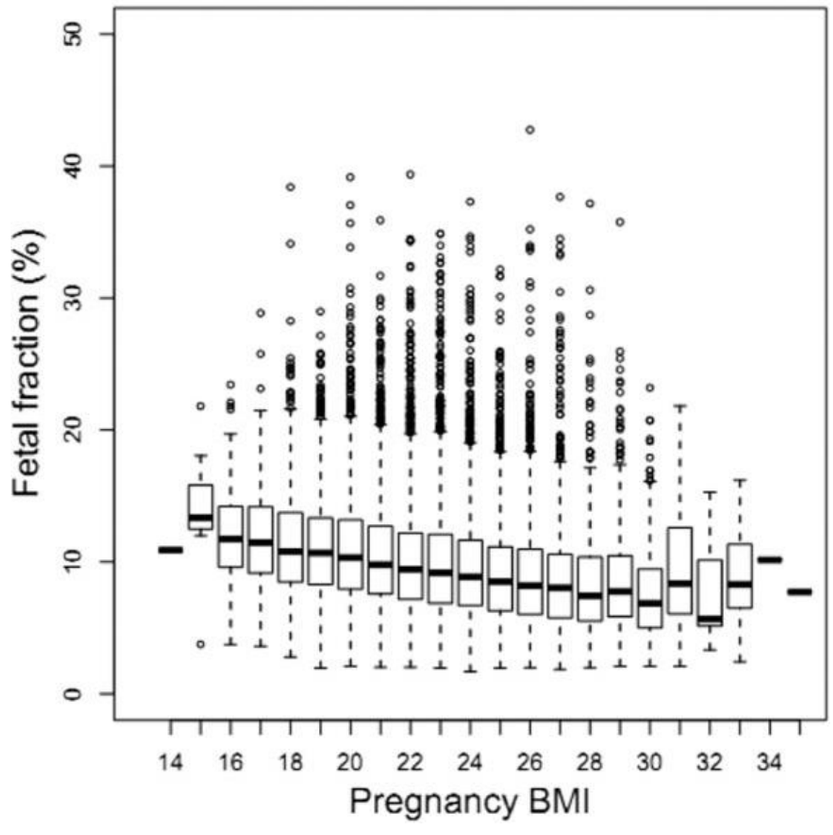

I Centri che erogano il test devono:

a) avere competenze nella diagnosi ecografica;

b) avere competenza nella diagnosi prenatale;

c) essere in grado di offrire la consulenza pre-test e post-test;

d) essere collegati con il laboratorio di cui al punto 8.

I Laboratori che eseguono il test devono:

a) essere certificati;

b) partecipare a programmi di controllo della qualità,

c) essere dotati di personale con competenza specifica nelle tecniche di NGS.

Nel caso in cui i laboratori sviluppino protocolli originali, è necessario che le tecniche e le procedure bioinformatiche siano rese pubbliche e disponibili alla validazione scientifica.

Per l’analisi delle aneuploidie mediante NIPT si utilizzano tre principali tecniche basate sulle tecniche di sequenziamento di seconda generazione (Next Generation Sequencing - NGS):

1) MPSS dell’intero genoma;

2) CSS di specifiche regioni;

3) SNP, cioè polimorfismi di singoli nucleotidi.

Gli studi relativi all'uso del NIPT come test di screening sono stati promossi e realizzati dalle aziende che, a partire dal 2012, hanno avviato la sua commercializzazione, con finalità cliniche:

Sequenom (MPSS-MaterniT21), Verinata (MPSS- Verifi), BGI (MPSS - NiftY G-TEST). (CSS- Harmony),
Natera (SNP - Panorama),

Il NIPT dove essere collegato e preceduto da un accurato controllo ecografico dopo l'XI settimana, effettuato da operatori accreditati nell'esame delle XI-XIV settimane.

Nel caso in cui i dati ecografici suggeriscano un aumento del rischio di patologia cromosomica nel feto, deve essere valutata l'opportunità di eseguire direttamente una diagnosi prenatale invasiva per lo studio del
cariotipo fetale, integrato eventualmente da altre tecniche

analisi costi benefici su un modello locale

Fonte: CEDAP

GRAVIDE MILANO 2012			*Dati Nicolaides (in corsivo)*
Età materna	**N. casi**	**N. Down attesi**	***Down attesi***
<20	206	0,1	*1/1600*
20	147	0,1	*1/1527*
21	239	0,2	*1/1483*
22	259	0,2	*1/1439*
23	348	0,2	*1/1395*
24	417	0,3	*1/1360*
25	472	0,3	*1/1352*
26	559	0,5	*1/1237*
27	689	0,6	*1/1123*
28	801	0,8	*1/1009*
29	918	1,0	*1/903*
30	1146	1,3	*1/895*
31	1332	1,7	*1/776*
32	1421	2,2	*1/659*
33	1439	2,6	*1/547*
34	1600	3,6	*1/446*
< 35 anni	**11.993**	**16**	

GRAVIDE MILANO 2012			*Dati Nicolaides (in corsivo)*
Età materna	**N. casi**	**N. Down attesi**	***Down attesi***
35	1676	4,7	**1/356**
36	1488	5,3	*1/280*
37	1575	7,2	*1/218*
38	1390	8,3	*1/167*
39	1192	9,3	*1/128*
40	972	10,0	*1/97*
41	716	9,8	*1/73*
42	421	7,7	*1/55*
43	305	7,4	*1/41*
44	180	6,0	*1/30*
45	112	4,9	*1/23*
46	60	3,5	1/17
47	33	2,1	1/16
48	14	0,9	1/15
49	15	1,5	1/10
≥50	12	1,2	1/10
≥ 35 anni	**10.161**	**90**	

TEST	Popolazione gravide Milano 2012	Costo totale	N. Down diagnosticati	N. Down non diagnosticati	N. Aborti Previsti
Età materna	10.161 (≥35)	**€4.064.400**	90/106	16/106	51-102
Test combinato	22.154	**€2.658.480**	95/106	11/106	6-12
Età materna + Test combinato	10.161 (≥35) 11.993 (<35)	**€5.722.880**	104/106	2/106	54-108
Test del DNA fetale	22.154	**€9.969.300**	105/106	1/106	0,5-1
Test combinato(*) + Test del DNA fetale	22.154	**€4.430.800**	**104/106**	**2/106**	**0,5-1**
NOTE Costo test combinato 100€-Costo amniocentesi 400€-Costo test DNA fetale 400€-N. Down atteso sulla popolazione gravide Milano 2012 106-Rischio aborto da amniocentesi 0,5/1%-					

(*) rischio intermedio 1/100-1/2000 = 20%