Diagnosi prenatale con test combinato : cosa cambia con la disponibilità del NIPT

Dott Armando Pintucci
UO Ostetricia e Ginecologia
Carate Brianza – Giussano
Università degli Studi di Milano-Bicocca

CENTRO ANALISI MONZA

corso ECM

LA NUOVA GENERAZIONE DI NIPT

martedì 10 maggio 2016
ore 18:00 - 22:00

Auditorium CAM Centro Analisi Monza
viale Elvezia · Monza

NIPT I° scelta o dopo test di screening convenzionali?

LINEE GUIDA SIEOG
Edizione 2015

Il test va integrato con le strategie di screening attuali non sostituendosi a queste.

Ogni gestante può decidere di sottoporsi a test invasivo, cfDNA test o nessun ulteriore test dopo calcolo del rischio individuale. Nuovi cut-off dovrebbero essere definiti su base locale/nazionale in relazione alle risorse disponibili e alle priorità del Sistema Sanitario Nazionale. Tuttavia, per un rischio particolarmente alto, oltre un cut-off da determinare, dovrebbe essere offerto solo un test diagnostico invasivo per l'alta percentuale di cromosomopatie che possono essere diverse da quelle diagnosticabili con il cfDNA test, in questo sottogruppo. In tale popolazione, inoltre, il tasso di falsi negativi del cfDNA test è elevato anche per le trisomie rilevabili dal test.

Global perspectives on clinical adoption of NIP

Mollie A. Minear[1], Celine Lewis[2], Subarna Pradhan[3] and Subhashini Chandrasekharan[3]*

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18

[redacted]

[redacted]

WHAT DOES THIS STUDY ADD?

- This study provides insight into worldwide availability of NIPT based on clinicians' experiences.
- The price of commercially available NIPT is limiting adoption, creating inequality of access.
- National and international policy deliberations are required to guide appropriate NIPT implementation worldwide.

Obstetrician and Gynecologist Utilization of the Noninvasive Prenatal Testing Expanded Option

Sarah Mayes, MS, CGC[1] Syed Hashmi, MD, MPH, PhD[2] Mark A. Turrentine, MD[3]
Sandra Darilek, MS, CGC[4] Lara A. Friel, MD, PhD[5] Jennifer Czerwinski, MS, CGC[5]

85 professionisti intervistati

Almeno 12aa di esperienza in medicina prenatale

If yes, how did you learn about expanded testing? Check all that apply. (n = 64)	
Medical literature	31 (48)
Professional society/conference	15 (23)
Colleague	[illegible]
Marketing from laboratories that offer it	30 (47)
Educational lecture	12 (19)
Other	2 (3)

Opt-in	19 (26)
No response	2 (3)

Practitioners need more information/education about the test/technology	77 (91)	3 (3)	2 (2)	3 (4)

Very comfortable	9 (11)

be?	
A screen	58 (68)

Conclusion Based on these findings and the fluid landscape of prenatal screening, education, and reeducation of health care professionals is imperative to ensure responsible patient counseling, informed consent, and appropriate posttest management.

2011 – Marzo 2016

8267 ***Donne hanno richiesto Screening e / o Diagnosi Prenatale Invasiva***

7874 Screening del 1 ° trimestre

800 procedure invasive (9.6 %)

2014 -- Marzo 2016

3149 ***Donne***

2975 Screening del 1 ° trimestre

108 Screening ad alto rischio (3.6 %)

282 Procedure invasive (8.9%)

Procedure invasive 282

Indicazione	N° ; %		Cario Reg N° ; %		An Crom N°; %		Tr 21 N°	Tr 13 N°	Tr 18 N°	Other N°
Età materna	149	**53%**	147	**98 %**	2	**2 %**	1	0	0	1§
Screening Alto Rischio	108	**38%**	89	**82 %**	19	**18 %**	14**	2	1	2***
Malformaz.	20	**7%**	17	**85 %**	3	**15 %**	1	1	1	0
Infezione	2	**0.7%**	//	//////	///	//////	//////	//////	//////	//////
DNA fetale *	3	**1.3%**	1	**33 %**	2	**67%**	0	1	0	1
TOT	282		254	**91%**	26	**8.9%**	16 **(63%)**	4 **(15%)**	2 **(7%)**	4 **(15%)**

* 1 Falso Positivo per Trisomia 13 ; 1 caso di 47 XXY § 1 caso di Trisomia del cr 7

** 1 Falso Negativo in Donna di 40 aa , con RR Tr21 1: 826 , NT 1,7 mm

*** 1 Trisomia del cr 9 ; 1 Delezione della regione 4p14.22q

Screening del 1 ° trimestre
Test combinato : NT +NB +FHR+ free BetaHcg + Papp-A
2975

Cut off Alto rischio Tr21 → 1:250 ; Tr13 / 18 → 1:50

Screening del primo trimestre ad Alto Rischio → 108

Risultato	NT ≥ 3.5 mm e/o RR Tr21 ≥ 1:50	NT regolare + 1:50 < RR Tr21 ≤ 100	NT regolare + 1: 100 < RRTr21 ≤ 1:250
	32	12	64
Cariotipo Reg.	16 (50 %)	11 (91.7 %)	63 (98.3 %)
Tr 21	12 (37.5 %)	1 (8.3 %)	0
Tr 13	1 (3.1 %)	0	1 (1.7 %)
Tr 18	1 (3.1 %)	0	0
Other	2 (6.3 %)	0	0

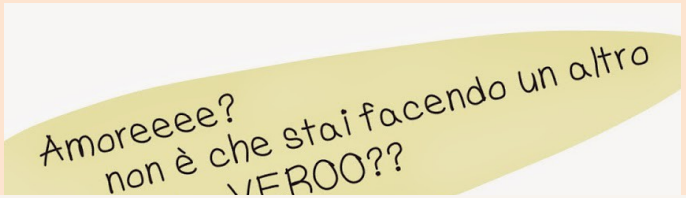
Ha senso proporre NIPT nello screening a basso rischio ?

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.



	Cell-free DNA Testing			
		All Patients (N=15,841)	Maternal Age <35 Yr (N=11,994)	Low Risk (N=14,957)†
True positive — no.	30	38	19	8
True negative — no.	14,949	15,794	11,969	14,941
False positive — no.	51	9	6	8
False negative — no.	0	0	0	0
Sensitivity (95% CI) — %	78.9 (62.7–90.4)	100 (90.7–100)‡	100 (82.4–100)	100 (63.1–100)
Specificity (95% CI) — %	[illegible]	[illegible]–100)§	99.9 (99.9–100)	99.9 (99.9–100)
Positive predictive value (95% CI) — %	3.4 (2.3–4.8)	80.9 (66.7–90.9)§	76.0 (54.9–90.6)	50.0 (24.7–75.3)
Negative predictive value (95% CI) — %	99.9 (99.9–100)	100 (99.9–100)¶	100 (99.9–100)	100 (99.9–100)

STUDIO NEXT

Studio prospettico in 35 Centri coinvolti

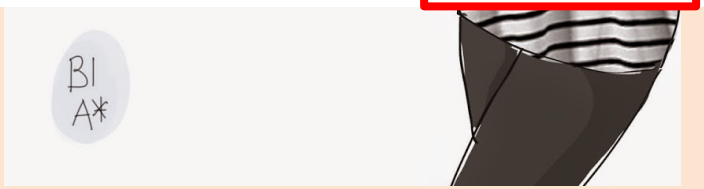
15841 donne valutate con Test comb vs NIPT

Anomalie cr identificate. Prevalenza → 1:236

Tr 21 ; Prevalenza → 1:417

Test combinato : sensibilità 79 % (cut off 1: 270)

falsi positivi 5.4 % (854 casi)



NIPT : sensibilità 100%

falsi positivi 0.06 % (9 casi)

Risultato assente nel 3 %

1868 NIPT per identificare 1 caso di Tr 21

NIPT test contingente per il Rischio Intermedio ?

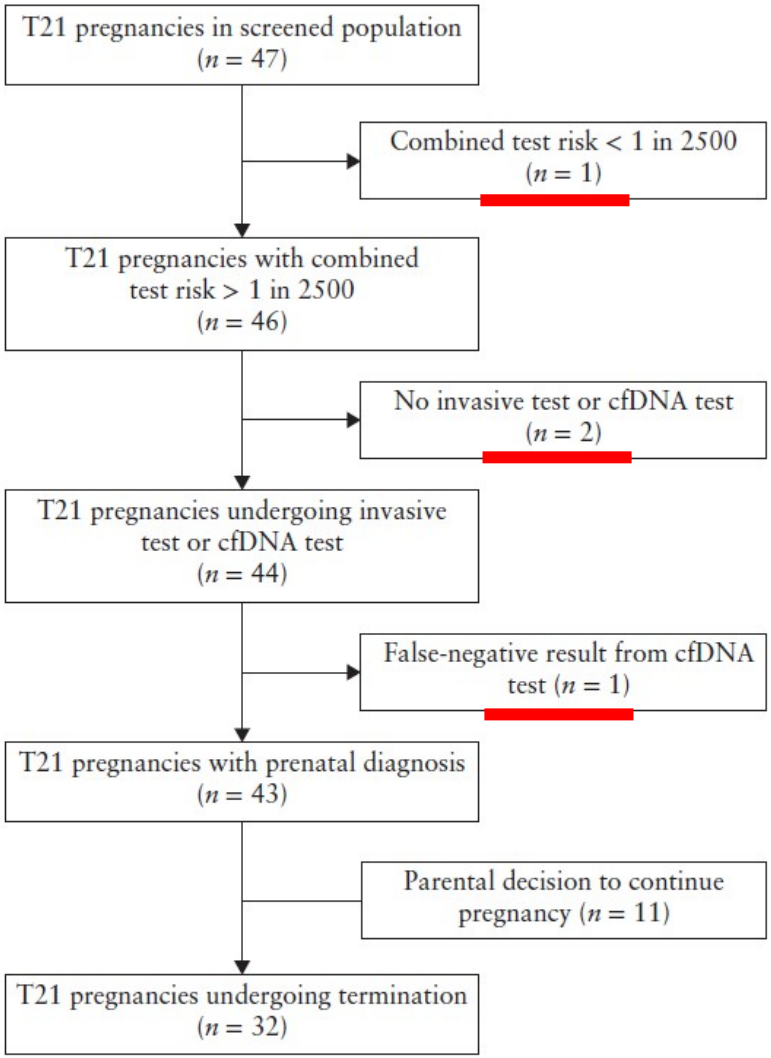


Figure 3 Flowchart summarizing prenatal diagnosis and management of pregnancies with fetal trisomy 21 (T21) in our study population of 11 692 women with singleton pregnancy.

3698 NIPT

11692 Screening con test combinato

RISCHIO INTERMEDIO 91.5 % opta NIPT

5 casi di Tr 21 (4 NIPT + 1 Non oltre procedure)

Sensibilità 99.7 %

Unico caso di Falso Negativo

Falsi PP >1: 100 tali 0.25 %

Sensibilità Tr 21 91.5 %

Sensibilità Tr13/Tr18 100%

Non risultato nel 1.7 %

Procedure Invasive 312

2.7 % del Totale (62.5 % x High Risk e/o NIPT +)

↓ nel High Risk del 43 % (60 % opta per NIPT)

NIPT test contingente per il Rischio Intermedio ?

Replacing the Combined Test by Cell-Free DNA Testing in Screening for Trisomies 21, 18 and 13: Impact on the Diagnosis of Other Chromosomal Abnormalities

Argyro Syngelaki[a] Eugene Pergament[b] Tessa Homfray[a] Ranjit Akolekar[c]
Kypros H. Nicolaides[a]

Rischio Test Combinato	NIPT	CVS	Detection Rate					
			Tr21	Tr13/18	XO	Sex An	Triploidia	Other
1:11-1:1000	12.8	0.8	95.9	97.5	74	3.4	28.6	6.8
1:51-1:1000	11.8	1.8	96.3	97.5	84	7.4	64.3	12.3
1:100-1:1000	10.8	2.9	96.3	98.1	86	8.1	89.3	13
1:11-1:2500	23.6	0.8	97.3	98.1	74	3.4	28.6	6.8
≤ 1:100	0	2.6	87	92	86	8.1	89.3	13

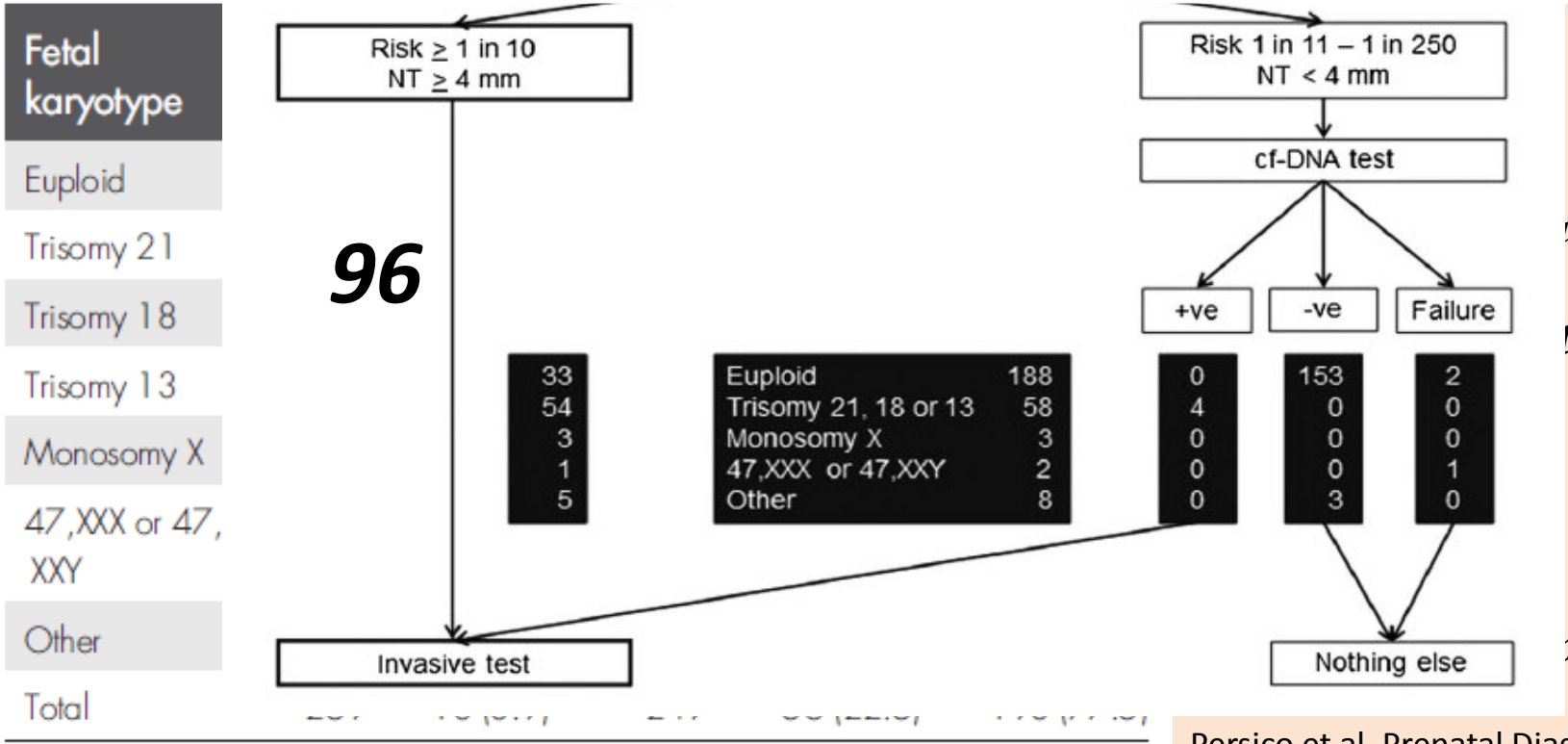
Almeno 80 % d ***74561 FTS*** ***Tr18***

14684 CVS → 2030 An Cr

Prevalenza delle Anom Cr me ***0 o se NT ≥ 3.5 mm***

Contingent NIPT perde 50 % delle Sex an ; il 50 % delle Other ; 1/3 delle Tripl.

Come può cambiare la valutazione dell' Alto rischio con NIPT



cfDNA, cell-free DNA.
Other = one case each of trisomy 4, trisomy 22, deletions in chromosomes 2, 4 and 16, duplication in chromosome 8, Beckwith-Wiedemann syndrome and monosomy 45X0/46XY.

Persico et al. Prenatal Diagnosis 2016

Tr21 ; Tr13 ; Tr 18 (100 %)

Alterazioni dei cr sessuali (80 %)

Altri difetti cromosomici (62.5%)

71 casi di anomalie cromosomiche (27.4 %)

8 casi anomali identificate con Array (11.3%)

188 casi di feti euploidi (72.6 %)

EVITARE PROC.INVASIVE NEL 82.5 % DEI FETI EUPLOIDI

Quale differenza nel Nostro Centro … ….

Risultato	NT ≥ 3.5 mm e/o RR Tr21 ≥ 1:10	NT regolare e < 1:10 RR Tr 21 ≤ 1: 250	
	17	91	
Cariotipo Reg.	4 (23.5%)	86	94.5 %
Tr 21	11(64.9%)	2	2.2 %
Tr 13	1 (5.8%)	1	1.1%
Tr 18	0(%)	1	1.1%
Other	1(5.8%) ***	1 **	1.1 %

NIPT

EVITARE procedura invasiva nel 95.5 % degli euploidi

Identificato il 100 % di Tr 21, Tr18, Tr13

50 % di identificazione di Altre An. Cromosomiche

*** 1 Delezione della regione 4p14.22q

** 1 Trisomia del cr 9

PRESENTATIONS FROM THE 2015 ISPD MEETING IN WASHINGTON, DC

Current controversies in prenatal diagnosis 3: is there still a value in a nuchal translucency screening ultrasound in conjunction with maternal plasma non-invasive cell-free DNA testing?†

R. Douglas Wilson[1*‡], Liona C. Poon[2‡] and Alessandro Ghidini[3‡]

Anatomia Fetale ***DR del 1° Trim → 53 %***

An cromosomiche rare ***VPP per An rare 0.05%***

Altri screening ***Low Papp-A alone ???***

UTILE CONTINUARE AD UTILIZZARE QUESTO SCREENING , LA CUI EFFICACIA è IN DISCUSSIONE E IL CUI PERCORSO COMPLESSO SPESSO INCREMENTA
ANSIA MATERNA IN GRAVIDANZA ?????????

1

What is the rc … hen with negative cell-f…

Emily S. Reiff[1,2,4*], … E.

2

DISCUSSION

In this study, we confirm that patients who screen negative for aneuploidy by cfDNA remain at risk for fetal structural supports that devastating structural defects that are not classically associated with the major trisomies will be missed if cfDNA is pursued without imaging between 11 and

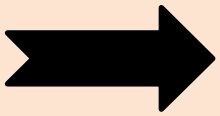
Table 2 Findings and outcomes of living fetuses with abnormal 11- to 14-week ultrasound

Findings at 11- to 14-week scan	NT ≥ 3.0 mm without cystic hygroma, no structural abnormality (range 3.0–4.0 mm)	NT ≥ 3.0 mm with cystic hygroma, no structural abnormality identified	NT ≥ 3.0 mm with structural abnormality	NT < 3.0 mm (or not measured) with structural abnormality
Total	26	4	3	4
Live birth, no abnormality	26	0	1[a]	0
Live birth with abnormality	0	1	0	0
Loss/IUFD	0	1	0	1
Termination	0	2	2	3
Diagnostic testing	7	2	2	3

NT, nuchal translucency; IUFD, intra-uterine fetal death.
[a]Anomaly resolved was a small omphalocele.

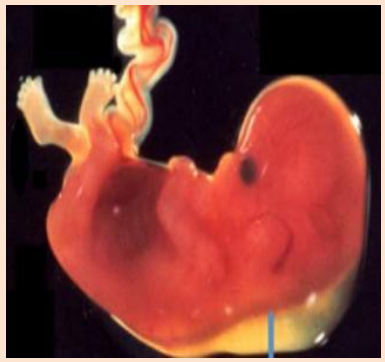
10 IUFD → 17 % ; 13 Twin ; 11 An Morfol → 19%

Studio retrospettico su 1739 pz
NIPT negativo
Valutaz Ecografica a 11-14 sett



Risultato inatteso in 60 / 1739 PZ → 3.5 %
14/ 1739 Procedure invasive 0.8%
1 Falso Negativo di Tr 18

Lost 1 / 1739 → 0.05 %



NIPT 1° screening

Studio retrospettico su 25.057 NT

10.7 % di All cromosomiche perse

Valutazione di An cromosomiche in NIPT 1° screening in NT group ≥ 3.5 mm

45.8 % Morte intrauterina

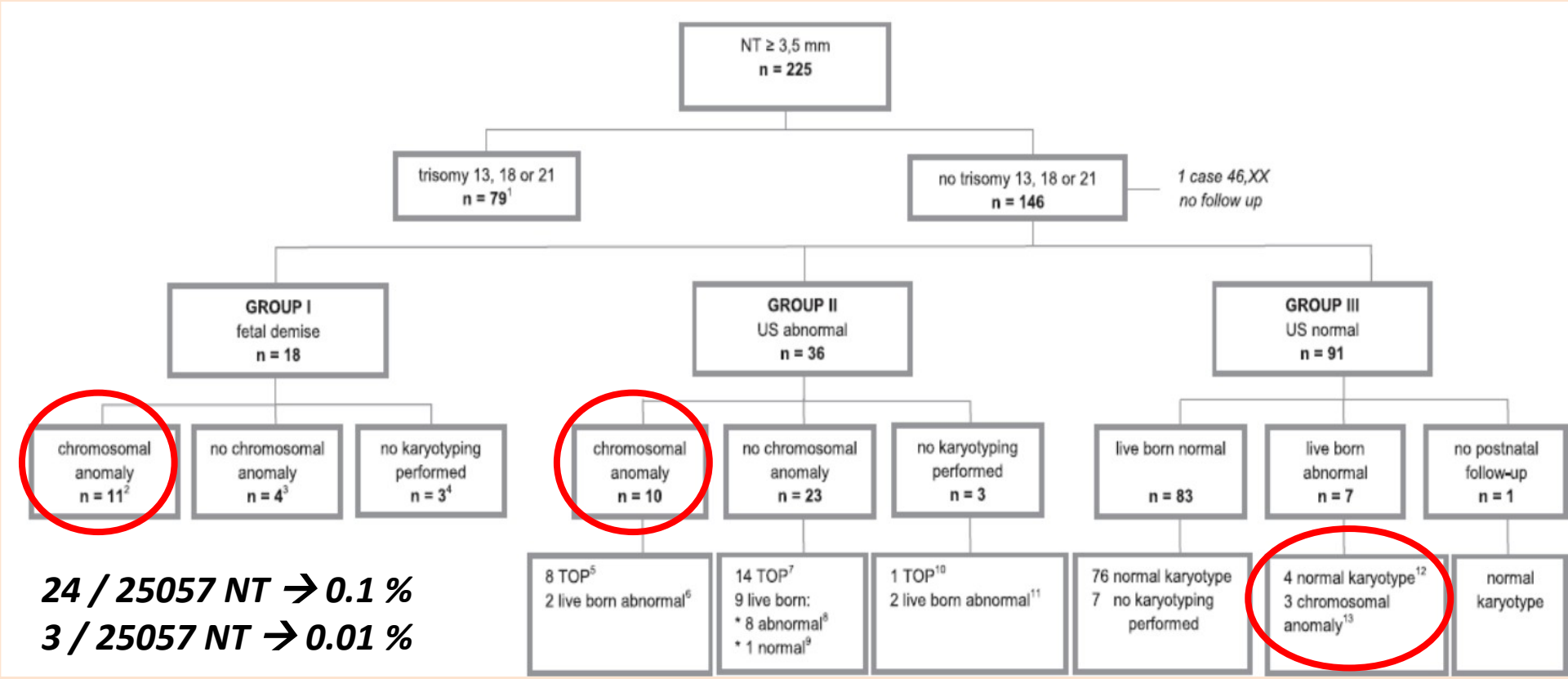
225 An. Cromosomiche → 77.7 % Tri 13/18/21

An. Morfologiche → 22.3 % Tri 13/18/21

III gruppi : Morte endouterina - Valutaz Eco al II tr - Valutaz Post

LOST : 47, XXX

2 delezioni de novo (Prader-Willy Syndrome)



24 / 25057 NT → 0.1 %

3 / 25057 NT → 0.01 %

Lichtenbelt K. D. et al. Prenatal Diagnosis 2015

Molecular Syndromology

Editorial – Late Breaking Chromosomes

Mol Syndromol 2015;6:153–155
DOI: 10.1159/000439237

Accepted: July 1, 2015
by M. Schmid
Published online: September 12, 2015

To NIPT or Not to NIPT ?

ARTICLE

Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe

Diana Wellesley*,[1], Helen Dolk[2], Patricia A Boyd[3], Ruth Greenlees[2], Martin Haeusler[4], Vera Nelen[5], Ester Garne[6], Babak Khoshnood[7], Berenice Doray[8], Anke Rissmann[9], Carmel Mullaney[10], Elisa Calzolari[11], Marian Bakker[12], Joaquin Salvador[13], Marie-Claude Addor[14], Elizabeth Draper[15], Judith Rankin[16] and David Tucker[17]

10323 ***Anomalia cromosomica***

Prevalenza Overall 43.8 / 10.000

Incidenza 7.4 / 10.000

European Journal of Human Genetics 2012;20:521-526

Chromosomal Abnormality	Characterized Detection by Noninvasive Prenatal Testing: Detectable	Not Detectable
T21		
Not mosaic	1,592	
Mosaic		18
T18		
Not mosaic	510	
Mosaic		7
T13		
Not mosaic	139	
Mosaic		4
Other trisomies		
Not mosaic		92
Mosaic		37
Sex chromosomal aneuploidy		
Not mosaic	246	
Mosaic		62
Balanced rearrangements		
Not mosaic		99
Mosaic		1
Unbalanced rearrangements		
Not mosaic		1
Insertions and deletions		
Not mosaic		88
Mosaic		5
Triploidy		
Not mosaic		30
Mosaic		1
Tetraploidy		
Mosaic		2
Extra structurally abnormal chromosome		
Not mosaic		9
Mosaic		5
Confined placental mosaicism		45
Total	2,487 (83.1)	506 (16.9)

Data are n or n (%).

Original Research

Chromosome Abnormalities Detected by Current Prenatal Screening and Noninvasive Prenatal Testing

Mary E. Norton, MD, Laura L. Jelliffe-Pawlowski, PhD, and Robert J. Currier, PhD

1.324.607 screening prenatali

68.

26.

244

560

CONCLUSION: For pregnant women with a positive aneuploidy screen who pursued diagnostic testing, 16.9% of chromosome abnormalities are not currently detectable by noninvasive prenatal testing. Undetectable aneuploidies range from relatively mild to those associated with significant disability. This is important information to be considered by patients, health care providers, and screening programs in evaluating the use of traditional screening and invasive prenatal diagnosis compared with noninvasive prenatal testing.

LEVEL OF EVIEDENCE: III

(Obstet Gynecol 2014;124:979–86)

53.1 % delle An cromosom → Tr 21

20-25 % delle An cromosom NON identifi → Q <35 aa

NT > solo nel 18.9 % delle An NON identificabili

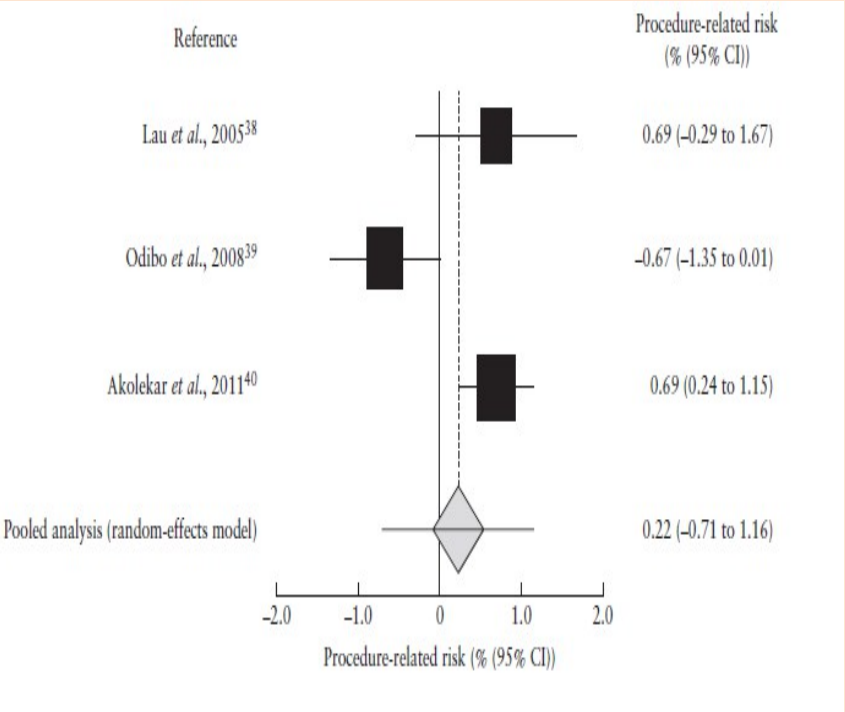
Ultrasound Obstet Gynecol 2015; 45: 16–26
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14636

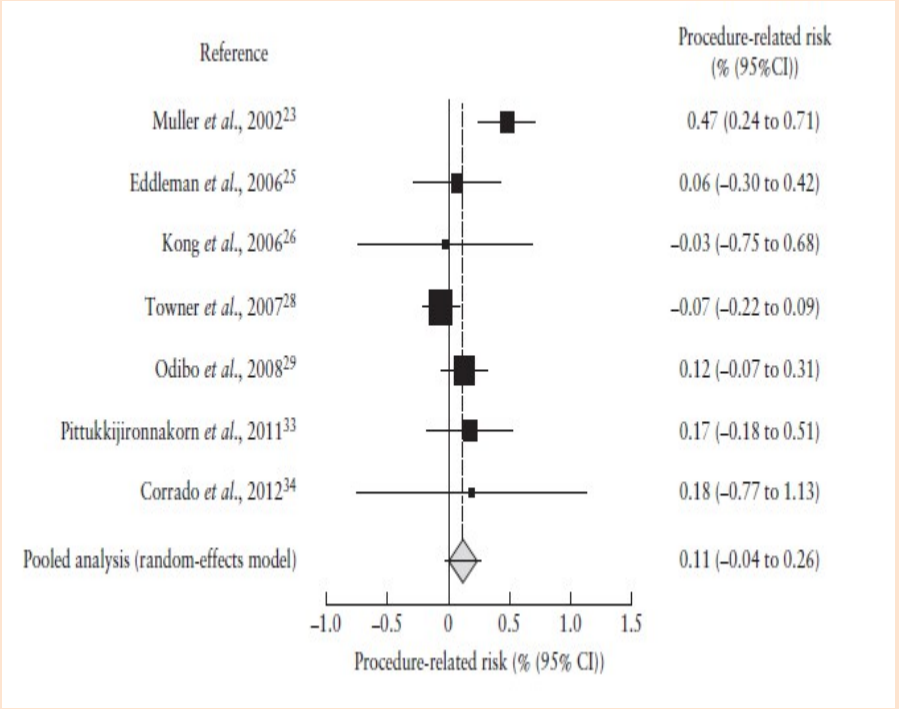
Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis

R. AKOLEKAR*†, J. BETA*, G. PICCIARELLI*, C. OGILVIE‡ and F. D'ANTONIO§

53890 done

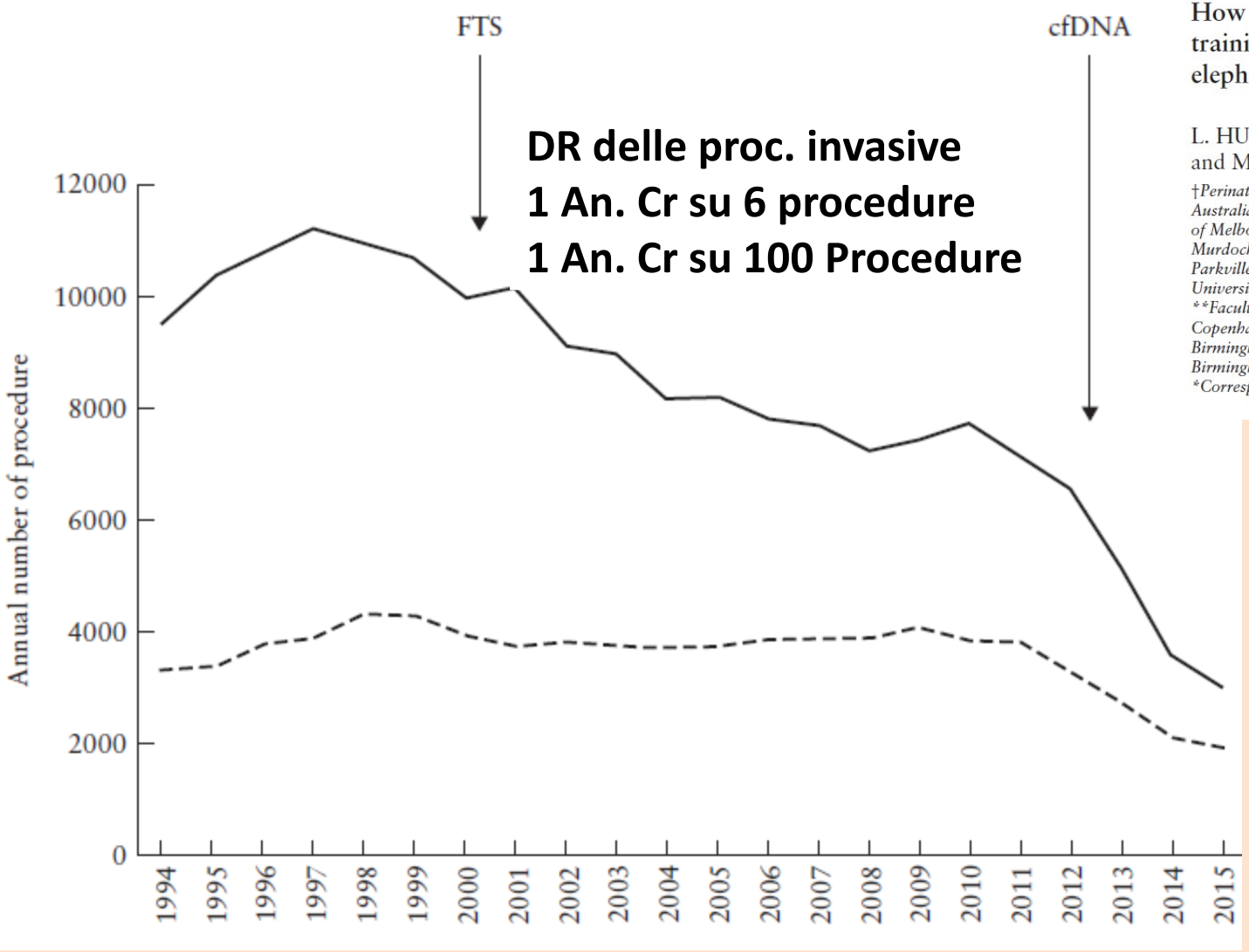
124001 donne





CVS 0.2 %

Amnio 0.1 %



How to safeguard competency and training in invasive prenatal diagnosis: 'the elephant in the room'

L. HUI*†‡§, A. TABOR¶**, S. P. WALKER†‡ and M. D. KILBY††

*†Perinatal Medicine, Mercy Hospital for Women, Heidelberg, VIC, Australia; ‡Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, VIC, Australia; §Public Health Genetics, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, VIC, Australia; ¶Center of Fetal Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; **Faculty of Medicine and Health Sciences, University of Copenhagen, Copenhagen, Denmark; ††Fetal Medicine Centre, Birmingham Women's Foundation Trust, and University of Birmingham, Birmingham, UK
Correspondence. (e-mail: lisahui77@gmail.com)

Royal College of Obstetricians & Gynaecologists

rti post procedura ←→ N° di Procedure /aa
N° di procedure per operatore / aa = 30.
/aa vs 1500 pr/ad OR 2.0 x fallimento proc.

Population Health Metrics

BioMed Central

Research

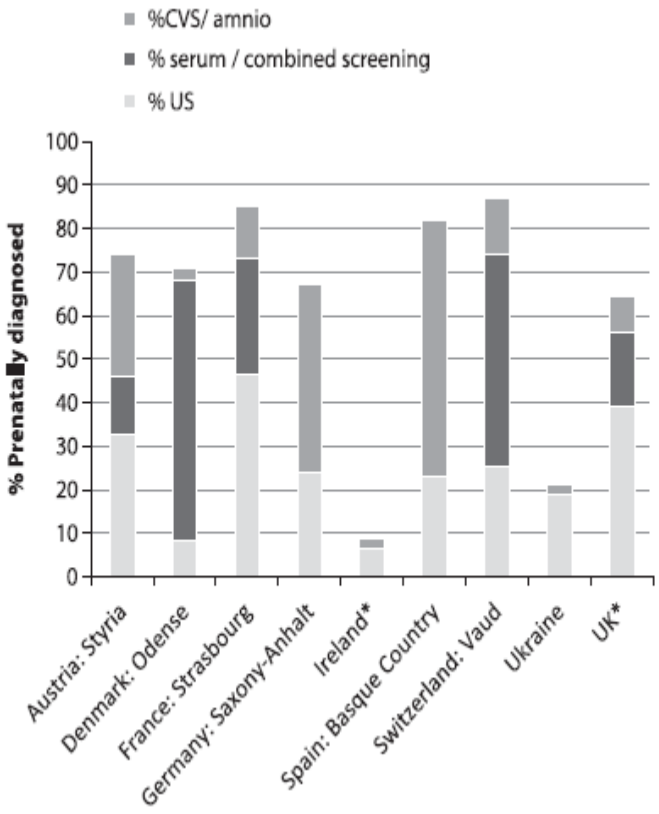
Open Access

Descriptive epidemiology of selected birth defects, areas of Lombardy, Italy, 1999

Chromosomal anomalies

Four boys (6.5/10,000) and six girls (10.2/10,000) had trisomy 21 or Down syndrome, the most commonly eported congenital autosomal anomaly.

Paolo Contiero[1]



Età < 19 aa nel 0.5 %

167.500 gravidanze > 35 aa

The rise in average maternal age in Europe over time has brought with it an increase in the number of pregnancies affected by trisomies 21, 18 and 13. However, the increasingly widespread practice of prenatal screening and termination of pregnancy has, on average, counteracted the effect of maternal age and resulted in a relatively stable LB prevalence of the major trisomies since 1990 in the European population studied. This is consistent with other studies

460 ***Casi identificati / aa***

10 casi persi per aa → Nati

Society for Maternal-Fetal Medicine

Society for Maternal·Fetal Medicine

1- *NIPT test di screening*
2- *Se Test positivo necessaria*

confema con procedura invasiva

3- *DR > FTS ma ricordare FP e FN*
4- *VPP a priori della donna deve essere considerato*
5- *Falsi positivi + frequenti se*

% di Fallimenti

Il tempo medio di risposta

Il Valore Predittivo Positivo

METHODS

At 21 centers in the United States, we collected blood samples from women with singleton pregnancies who were undergoing standard aneuploidy screening (serum biochemical assays with or without nuchal translucency measurement). We performed massively parallel sequencing in a blinded fashion to determine the chromosome dosage for each sample. The primary end point was a comparison of the false positive rates of detection of fetal trisomies 21 and 18 with the use of standard screening and cfDNA testing. Birth outcomes or karyotypes were the reference standard.

RESULTS

The primary series included 1914 women (mean age, 29.6 years) with an eligible sample, a singleton fetus without aneuploidy, results from cfDNA testing, and a risk classification based on standard screening. For trisomies 21 and 18, the false positive rates with cfDNA testing were significantly lower than those with standard screening (0.3% vs. 3.6% for trisomy 21, P<0.001; and 0.2% vs. 0.6% for trisomy 18, P=0.03). The use of cfDNA testing detected all cases of aneuploidy (5 for trisomy 21, 2 for trisomy 18, and 1 for trisomy 13; negative predictive value, 100% [95% confidence interval, 99.8 to 100]). The positive predictive values for cfDNA testing versus standard screening were 45.5% versus 4.2% for trisomy 21 and 40.0% versus 8.3% for trisomy 18.

CONCLUSIONS

In a general obstetrical population, prenatal testing with the use of cfDNA had significantly lower false positive rates and higher positive predictive values for detection of trisomies 21 and 18 than standard screening. (Funded by Illumina; ClinicalTrials.gov number, NCT01663350.)

and specificities (Table 3). PPV, positive predictive value

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 27, 2014 VOL. 370 NO. 9

DNA Sequencing versus Standard Prenatal Aneuploidy Screening

Diana W. Bianchi, M.D., R. Lamar Parker, M.D., Jeffrey Wentworth, M.D., Rajeevi Madankumar, M.D., Craig Saffer, M.D., Anita F. Das, Ph.D., Joseph A. Craig, M.D., Darya I. Chudova, Ph.D., Patricia L. Devers, M.S., C.G.C., Keith W. Jones, Ph.D., Kelly Oliver, B.S., Richard P. Rava, Ph.D., and Amy J. Sehnert, M.D., for the CARE Study Group*

VPP per Tr 13 / 18 è < Tr 21

VPP dip. dal Rischio a priori

Rischio a priori → Multifattoriale

An. Cr. Rare rischio a priori basso

Donne a Basso rischio

VPP x Tr 21 del 45.5 %

VPP → x Tr° 18 del 40 %

Risultato positivo deve essere sempre confermato da indagine invasiva


Australian Institute of
Caring for people
Professional Counsellors
KEEP
CALM
AND
STUD
COUNSEL
THANK YOU
THANK YOU
THANK YOU