Diagnostica prenatale invasiva: c'è ancora un ruolo?

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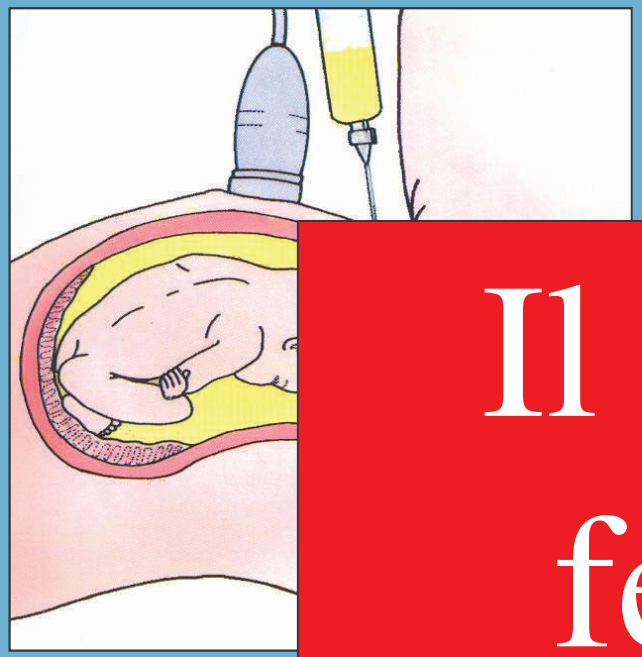
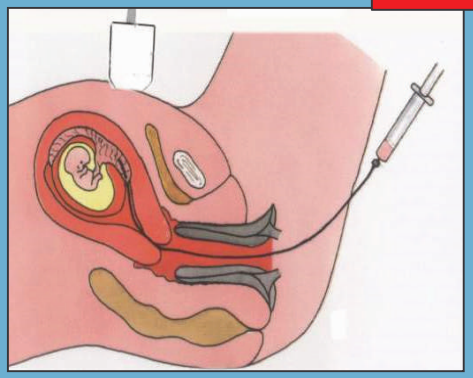
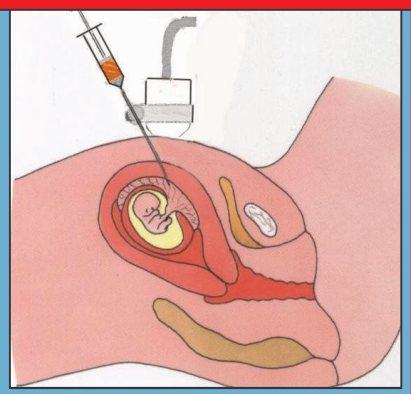
Diagnosi prenatale: ieri ed oggi



I test di Screening

Il DNA fetale





enetica

vs

Molecolare

Dai nuovi LEA 2017 per la gravidanza

ALLEGATO 10C

CONDIZIONI DI ACCESSO ALLA DIAGNOSI PRENATALE INVASIVA, IN ESCLUSIONE DALLA QUOTA DI PARTECIPAZIONE AL COSTO

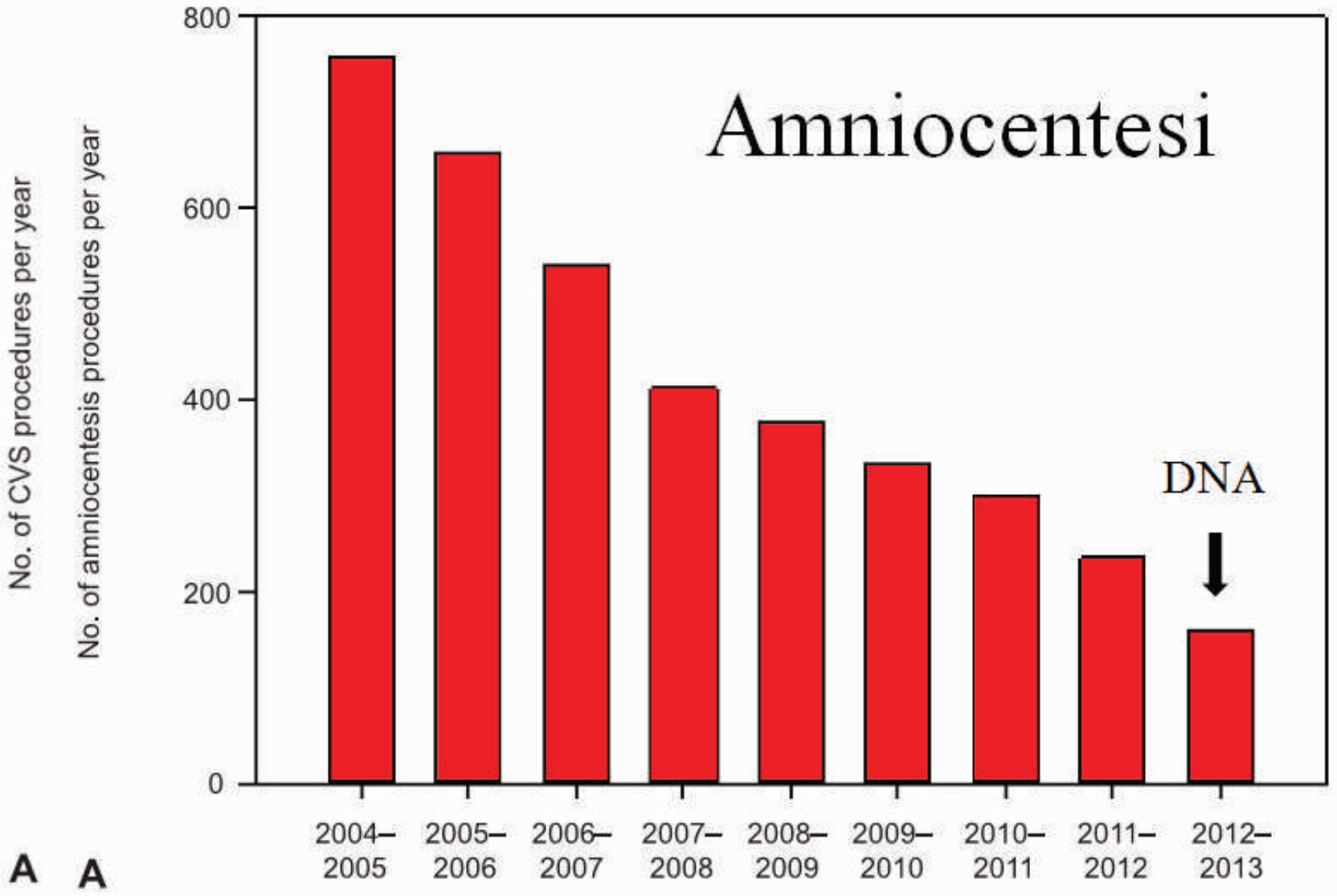
1)

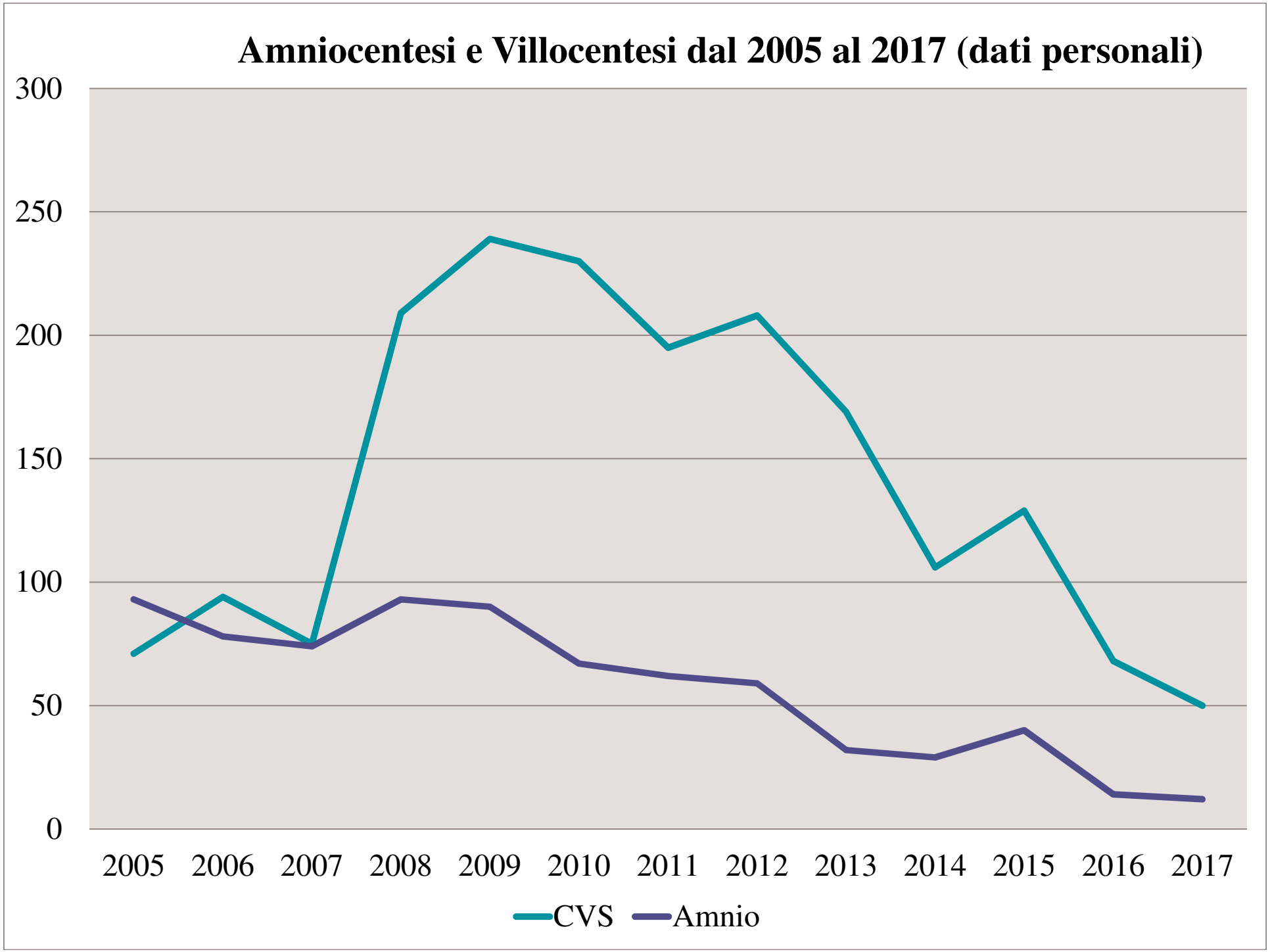
- probabilità di trisomia 21, o di altre anomalie cromosomiche ≥1/300 al momento del test per la valutazione del rischio nel primo trimestre (o ≥1/250 in caso di test nel secondo trimestre)
-
-
-
- anomalie fetali della gravidanza evidenziate mediante ecografia

Association of Combined First-Trimester Screen and Noninvasive Prenatal Testing on Diagnostic Procedures

Sebastian Larion, MS, Steven L. Warsof, MD, Letty Romary, MD, Margaret Mlynarczyk, MD, PhD, David Peleg, MD, and Alfred Z. Abuhamad, MD

(Obstet Gynecol 2014;123:1303–10)




Amniocentesi e Villocentesi dal 2005 al 2017 (dati personali)
300
250
200
150
100
50
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
CVS
Amnio

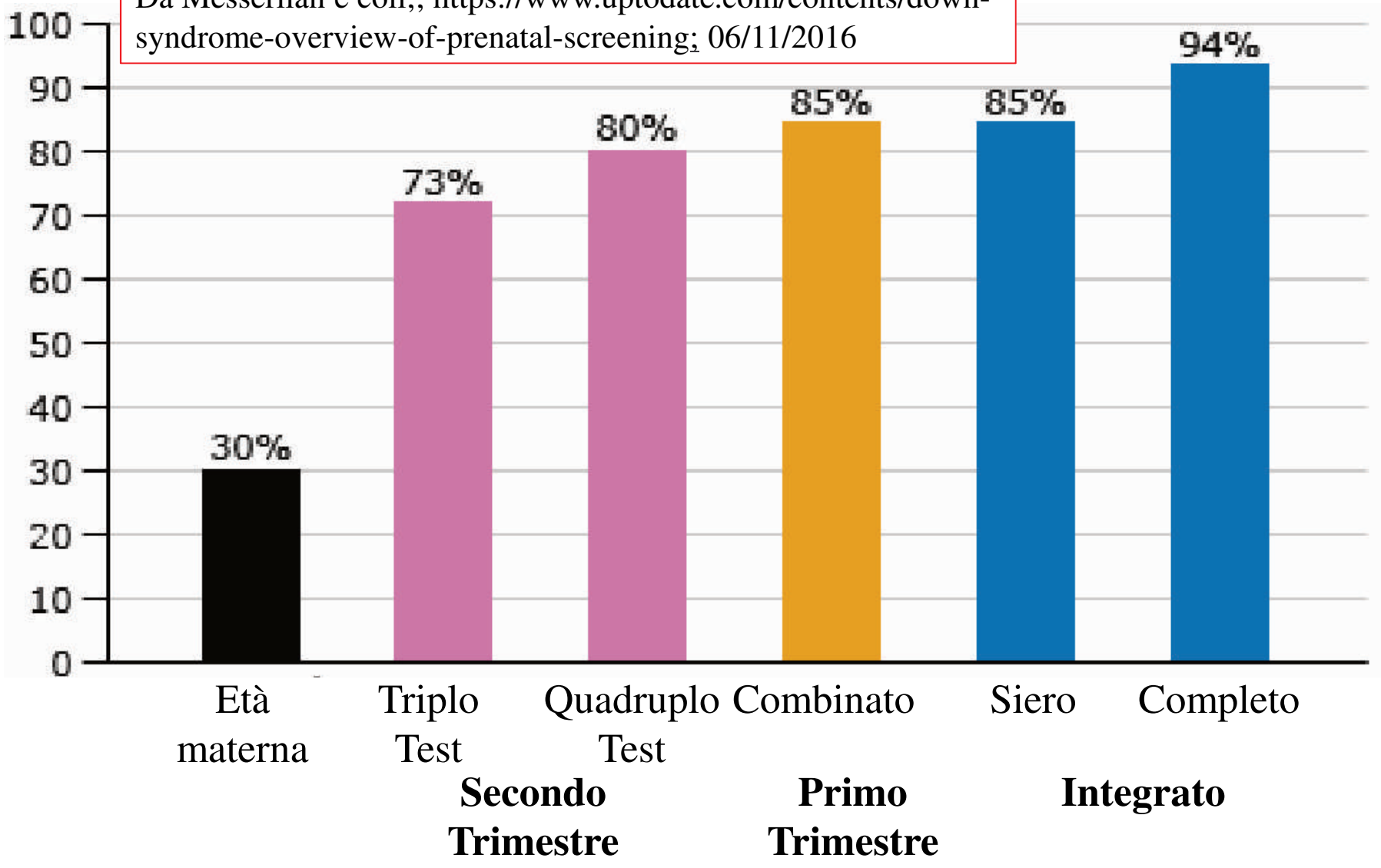
Screening vs Diagnosi prenatale invasiva?

Pro	Contro
Assenza di rischi	Spettro diagnostico limitato*
Applicazione su larga scala	Possibilità di falsi negativi e positivi
Ripetibilità	Criteri di interpretazione non sempre chiari
Costi minori (?)	Eventuale ritardo nella diagnosi definitiva

*Trisomia 21,13,18 – 45,X- 47,XXY-47,XXX-47,XYY (con DNA)

Detection rate dell'età materna e dei test di screening biochimici della trisomia 21 (5% falsi positivi)

Da Messerlian e coll;; https://www.uptodate.com/contents/down-syndrome-overview-of-prenatal-screening; 06/11/2016



Attendibilità dello screening con DNA fetale in recenti meta-analisi

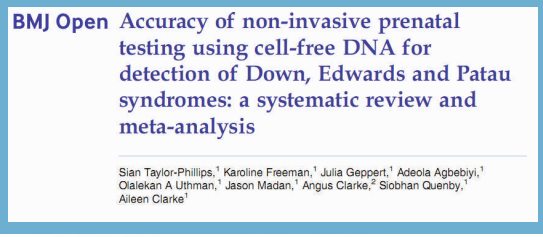

AOGS Acta Obstetricia et Gynecologica Scandinavica

Systematic Review

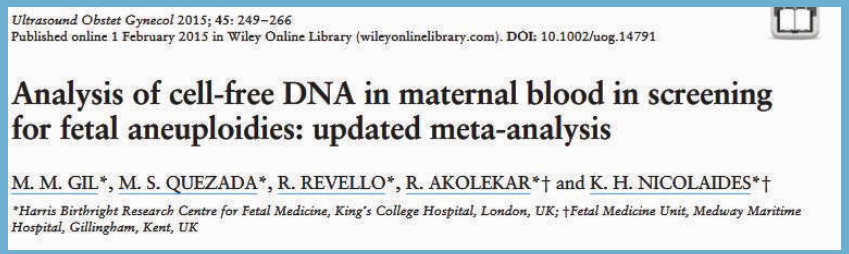
Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population – a systematic review and meta-analysis

Erik Iwarsson, Bo Jacobsson, Jessica Dagerhamn, Thomas Davidson, Eduardo Bernabé, Marianne Heibert Arnlind

First published: 25 October 2016 | https://doi.org/10.1111/aogs.13047 | Cited by: 10


BMJ Open Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis

Sian Taylor-Phillips,[1] Karoline Freeman,[1] Julia Geppert,[1] Adeola Agbebiyi,[1] Olalekan A Uthman,[1] Jason Madan,[1] Angus Clarke,[2] Siobhan Quenby,[1] Aileen Clarke[1]


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*†

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


BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14050
www.bjog.org

Systematic review

The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis

FL Mackie,[a] K Hemming,[b] S Allen,[c] RK Morris,[a,d] MD Kilby[a,d]

- **T21 - DR 99,5% FPR 0,05%**
- **T18 - DR 97,7% FPR 0,04%**
- **T13 - DR 96,1% FPR 0,06%**

- **45,X - DR 90,3% FPR 0,23%**
- **47XXX, 47XXY, 47XYY : DR 93,0% FPR 0,14%**

GEMELLARI:

- **T21 - DR 98,7% FPR 0,11%**
- **T18 : 13/14 T13 : 2/3**

DR= detection rate
FPR= false positive rate

Valori predittivi positivi (PPV e negativi (NPV) dei test di screening prenatali (da Glenn e coll. Curr.Op.Obst&Gyn 08/2018)

		Popolazione Generale		Età > 35 anni	
Anomalia	**Test**	**PPV**	**NPV**	**PPV**	**NPV**
Trisomia 21	Combinato	5% **(1:19)**	99,9% **(2500:1)**	12% **(1:9)**	99,9% **(943:1)**
Trisomia 21	DNA	71% **(2:1)**	99,9% **(>50000:1)**	87% **(7:1)**	99,9% **(25000:1)**
Trisomia 18	DNA	56% **(1:2)**	99,9% **(>50000:1)**	63% **(1:1)**	99,9% **(26000:1)**
Monosomia X	DNA	12% **(1:8)**	99,9% **(2400:1)**	12% **(1:8)**	99,9% **(2400:1)**

Principali problemi nello screening con DNA fetale

- **Fallimento dell'esame: 1-5%** (frazione fetale insufficiente <4%)
  - ✓Età gestazionale < 10 settimane
  - ✓Prelievo errato
  - ✓Obesità materna (> 80 kg)
  - ✓Anomalie cromosomiche fetali (13-18, X0, Triploidie)
- **Falso positivo:**
  - ✓Mosaicismo placentare
  - ✓"Vanishing twin"
  - ✓Anomalie cromosomiche materne costituzionali o acquisite (mosaicismi, anomalie strutturali,neoplasie, trapianti, trasfusioni recenti...)
- **Falso negativo:**
  - ✓Mosaicismo placentare
  - ✓Frazione fetale borderline

Diagnostica prenatale invasiva: c'è ancora un ruolo?

- Positività del test di screening
- Patologie a rischio di ricorrenza (cromosomiche o geniche)
- Gemellarità (?)
- Rilievo ecografico di anomalie fetali*
- Infezioni in gravidanza

CVS > Amniocentesi

Amniocentesi > CVS *Preferibile CGH array (cariotipo molecolare)

Vantaggi della tecnica CGH array

- Spettro diagnostico più ampio rispetto al cariotipo convenzionale
  - *+1,7% di anomalie rilevate in casi senza malformazioni ecografiche*
  - *+6,5% di anomalie rilevate in casi con malformazioni ecografiche*
- Possibilità di analisi diretta senza coltura
  - *Utilizzabile anche in caso di MEF e mortalità neonatale*
- Tempi di risposta più rapidi

Svantaggi e della tecnica CGH array

- Incapacità di rilevare anomalie cromosomiche bilanciate, disomie uniparentali, mosaicismi
- Rilievo di varianti di significato incerto
- Costi più elevati

Indicazioni preferenziali della tecnica CGH array in ostetricia

- Valutazione di feti con sindromi malformative o difetti di crescita rilevati all'ecografia
- Casi di MEF (in cui si ritenga indicata l'indagine cromosomica)
- Conferma di microdelezioni rilevate con il DNA fetale

• *Alternativa al cariotipo tradizionale?*

Sindromi da microdelezione diagnosticabili con CGH array

43 varianti con piattaforma Easychip

Syndromic regions	incidence	critical genes
1p36 deletion syndrome	1/5,000	/
1q41q42 microdeletion syndrome	unknown	DISP1
2p15-16.1 microdeletion syndrome	unknown	BCL11A
2q23.1 microdeletion syndrome	unknown	MBD5, EPC2
2q33.1 deletion (Glass syndrome)	unknown	STAB2
2q37 deletion syndrome	<1/10,000	HDAC4
3pter-p25 deletion syndrome	unknown	CNTN4, ITPR1, SRGAP3, VHL
3q29 deletion/duplication syndrome	unknown	FBXO45, PAK2, DLG1
4p16.3 deletion syndrome (Wolf-Hirschhorn)	1/20,000 - 1/50,000	LETM1, WHSC1
4q21 deletion syndrome	unknown	PRKG2, RASGEF1B
5p deletion syndrome (Cri du chat)	1/20,000 – 1/50,000	CTNND2, TERT
5q14.3 deletion syndrome	unknown	MEF2C
5q35 deletion syndrome (Sotos)	1-9/100,000	NSD1
6q13-q14 deletion syndrome	unkown	COL12A1
7q11.23 deletion syndrome (Williams-Beuren)	1/10,000	ELN
8p23.1 deletion syndrome	unknown	GATA4
8q21.11 Microdeletion Syndrome	unknown	ZFHX4, PEX2
8q24.1 deletion syndrome (Langer-Giedion)	unknown	TRPS1, EXT1
9q34.3 deletion syndrome (Kleefstra)	unknown	EHMT1
10p14p13 deletion syndrome (DiGeorge type 2)	unknown	GATA3
11p13 deletion syndrome (WAGR)	unknown	PAX6, WT1
11p11.2 deletion syndrome (Potocki-Shaffer)	unknown	ALX4
11q deletion syndrome (Jacobsen)	1/100,000	/
14q12 microdeletion syndrome	unknown	FOXG1
15q11q13 deletion syndrome (Prader-Willi)	1/25,000	SNRPN
15q11q13 deletion syndrome (Angelman)	1/10,000 - 1/20,000	UBE3A
15q24 deletion/duplication syndrome	unknown	/
16p deletion syndrome (ATR-16)	unknown	HBA1, HBA2
16q24.1 micorodeletion syndrome	unknown	FOXF1, FOXC2
17p13.3 deletion syndrome (Miller dieker)	unknown	PAFAH1B1, YWHAE
17p11.2 deletion syndrome (Smith-Magenis)	1/25,000	RAI1
17p11.2 duplication syndrome (Potocki Lupski)	unkown	RAI1
17q11.2deletion/duplication syndrome	unkown	NF1, SUZ12
17q21.31 deletion syndrome (Koolen-De Vries)	1/16,000	KANSL1
17q23.1-q23.2 deletion syndrome	unknown	TBX2, TBX4
19q13.11 deletion syndrome	unknown	LSM14A, UBA2
Down Sndrome critical region (21q22.12q22.2)	1/650 - 1,000	/
22 partial tetrasomy (Cat eye)	1/50,000 - 1/150,000	/
22q11.2 deletion syndrome (DiGeorge)	1/2,000 – 1/4,000	HIRA, TBX1
22q11.2 distal deletion syndrome	unknown	MAPK1
Xp11.3 deletion syndrome	unknown	RP2
Xp11.22 microduplication syndrome	unknown	HUWE1
Xq12 deletion/duplication (OPHN1)	unknown	OPHN1
Xq22.3 deletion syndrome (AMME COMPLEX)	unknown	COL4A5, ACS4
Xq28 duplication syndrome	unknown	MECP2

Alesi et al., J Genet Syndr Gene Ther 2016, 7:1

Diagnostica prenatale invasiva: c'è ancora un ruolo?

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Rifiuto o riconsiderazione del test di screening da parte della gravida

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

Society for Maternal-Fetal Medicine

(Published Electronically Ahead of Print on March 1, 2016)

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 163, MAY 2016

(Replaces Practice Bulletin Number 77, January 2007)
(See also Practice Bulletin Number 162, *Prenatal Diagnostic Testing for Genetic Disorders*)

Screening for Fetal Aneuploidy

values. Obstetrician–gynecologists and other obstetric care providers should become familiar with the available screening and diagnostic testing options for their patients within their practice and adopt a standard approach for counseling. Regardless of which screening tests are offered, information about the detection (sensitivity) and positive screening and false-positive rates, advantages, disadvantages, and limitations should be communicated to the patient. At the time of counseling regarding aneuploidy screening, the benefits and risks of diagnostic testing (amniocentesis and chorionic villus sampling) also should be discussed (29). After counseling, patients may decline screening or diagnostic testing for any reason.

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§

Only studies reporting data on more than 1000 procedures were included in this review

ABSTRACT

included in this review to minimize the effect of bias from smaller studies. Heterogeneity between studies was estimated using Cochran's Q, the I^2 statistic and Egger bias. Meta-analysis of proportions was used to derive weighted pooled estimates for the risk of miscarriage before 24 weeks' gestation. Incidence–rate difference meta-analysis was used to estimate pooled procedure-related risks.

Results The weighted pooled risks of miscarriage follow-

(95% CI, 0.46–0.91%) for amniocentesis and 1.79% (95% CI, 0.61–3.58%) for CVS. The weighted pooled procedure-related risks of miscarriage for amniocentesis and CVS were 0.11% (95% CI, –0.04 to 0.26%) and 0.22% (95% CI, –0.71 to 1.16%), respectively.

***Conclusion** The procedure-related risks of miscarriage following amniocentesis and CVS are much lower than are currently quoted.*

The weighted pooled procedure-related risks of miscarriage for amniocentesis and CVS were 0.11% (95% CI, –0.04 to 0.26%) and 0.22% (95% CI, –0.71 to 1.16%), respectively.

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NUMBER 162, MAY 2016

(Replaces Practice Bulletin Number 88, December 2007)
(See also Practice Bulletin Number 163, *Screening for Fetal Aneuploidy*)

Prenatal Diagnostic Testing for Genetic Disorders

The rate of procedure-related pregnancy loss that is attributable to a prenatal diagnostic procedure currently is estimated to be approximately 0.1–0.3% in procedures performed by experienced health care providers. The loss rates for amniocentesis and CVS are both very low.

Royal College of Obstetricians and Gynaecologists

Competency should be maintained by carrying out at least 30 ultrasound guided invasive procedures per annum.

integral part of training.

Very experienced operators (more than 100 per annum) may have a higher success rate and a lower procedure-related loss rate. Occasional operators who perform a low number of procedures per annum may have increased rates of procedure-related loss.


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LA PREGO...
STIA FERMA!!!
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202...