Genetica Prenatale in ostetricia: Stato dell'arte

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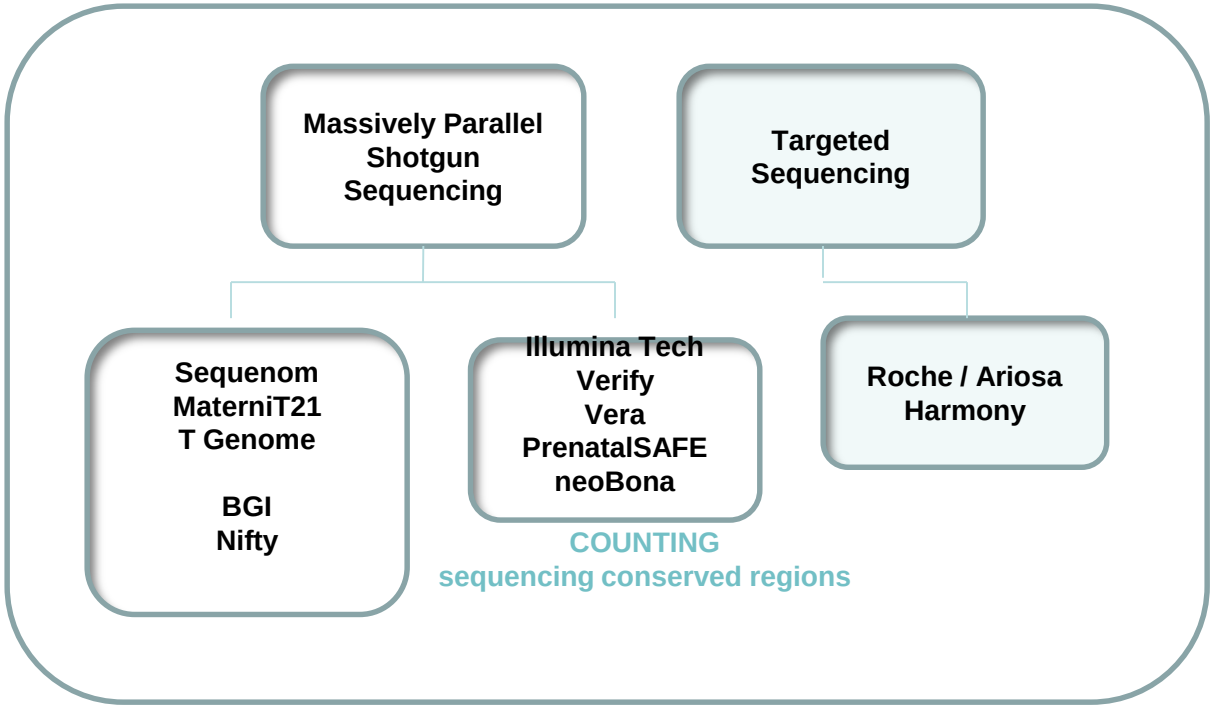
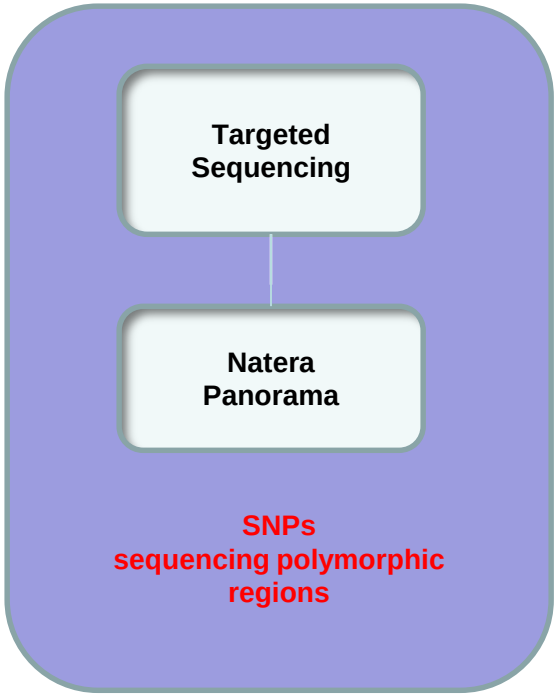
Le classiche NIPT Methodologies: SNPs vs. Counting





Attuali differenze fra Counting e SNPs

- Ovodonazioni: **COUNTING**
- Vanishing Twin : **COUNTING**
- Genome Wide (7-10 Mb): **COUNTING**
- Pz. Politrasfuse : **COUNTING**
- Triploidia: **SNPs**
- Zigosità: **SNPs**
- S. di Di George e pannello microdelezioni: **SNPs vs. DANSR, TCEA , Counting**
- Malattie mendeliane dominanti *de novo* e recessive **??**

Items for today

- Test sequenziale «reflex» Test combinato + DNA fetale
- La integrazione NT e NIPT
- Confronto delle performance dello screening della Sindrome di DiGeorge
- I pannelli per le malattie mendeliane

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Test sequenziali vs. Down

- Il primo test deve essere molto sensibile
- Il secondo test deve essere molto specifico

- Il test combinato è meno specifico e meno sensibile del DNA fetale
- La sensibilità del test combinato è tarata su 5% circa di FPR (1:300)
- Per rendere il test combinato più sensibile il cut-off va spostato a livelli simili o superiori a quelli della incidenza generale (1:700)

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*

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

Table 3 Distribution of risk from the combined test in 11 692 women with singleton pregnancy attending National Health Service hospitals, according to trisomic outcome

Risk cut-off	*Trisomy 21 (n = 47)*	*Trisomy 18 (n = 24)*	*Trisomy 13 (n = 4)*	*Unaffected (n = 11 617)*
≥ 1 in 10	30 (63.8)	19 (79.2)	4 (100)	62 (0.5)
≥ 1 in 20	36 (76.6)	20 (83.3)	4 (100)	101 (0.9)
≥ 1 in 50	38 (80.9)	21 (87.5)	4 (100)	208 (1.8)
≥ 1 in 100	41 (87.2)	22 (91.7)	4 (100)	393 (3.4)
≥ 1 in 500	46 (97.9)	23 (95.8)	4 (100)	1351 (11.6)
≥ 1 in 1000	46 (97.9)	24 (100)	4 (100)	2181 (18.8)
≥ 1 in 1500	46 (97.9)	24 (100)	4 (100)	2870 (24.7)
≥ 1 in 2000	46 (97.9)	24 (100)	4 (100)	3429 (29.5)
≥ 1 in 2500	46 (97.9)	24 (100)	4 (100)	3938 (33.9)
≥ 1 in 3000	46 (97.9)	24 (100)	4 (100)	4453 (38.3)
≥ 1 in 3500	47 (100)	24 (100)	4 (100)	4899 (42.2)

Data are given as *n* (%).

Original Article

Performance of antenatal reflex DNA screening for Down's syndrome

J Med Screen
2015, Vol. 22(4) 168–174

DOI: 10.1177/0969141315581005
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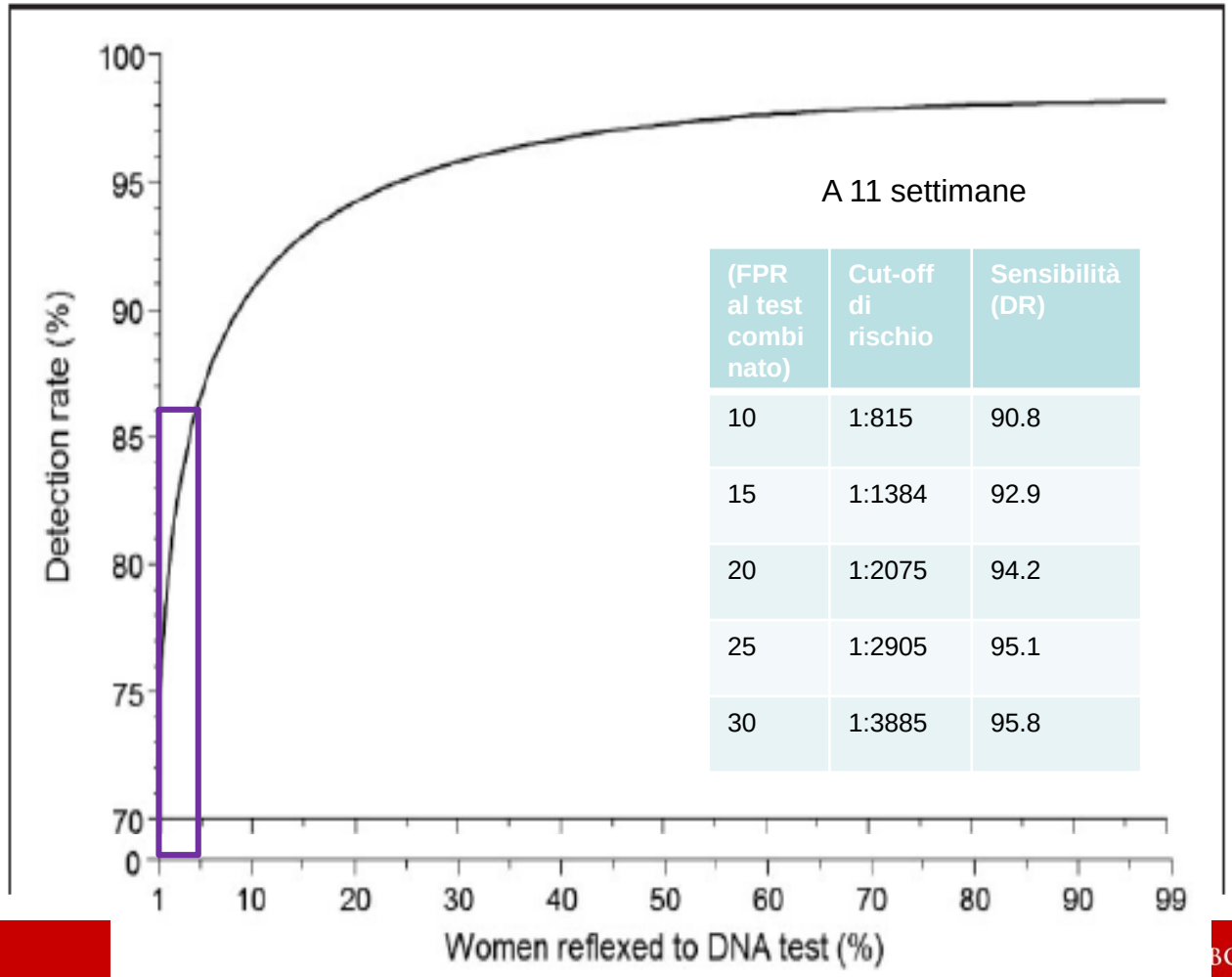
Nicholas J Wald and Jonathan P Bestwick



A 11 settimane

(FPR al test combinato)	Cut-off di rischio	Sensibilità (DR)
10	1:815	90.8
15	1:1384	92.9
20	1:2075	94.2
25	1:2905	95.1
30	1:3885	95.8

Original Article

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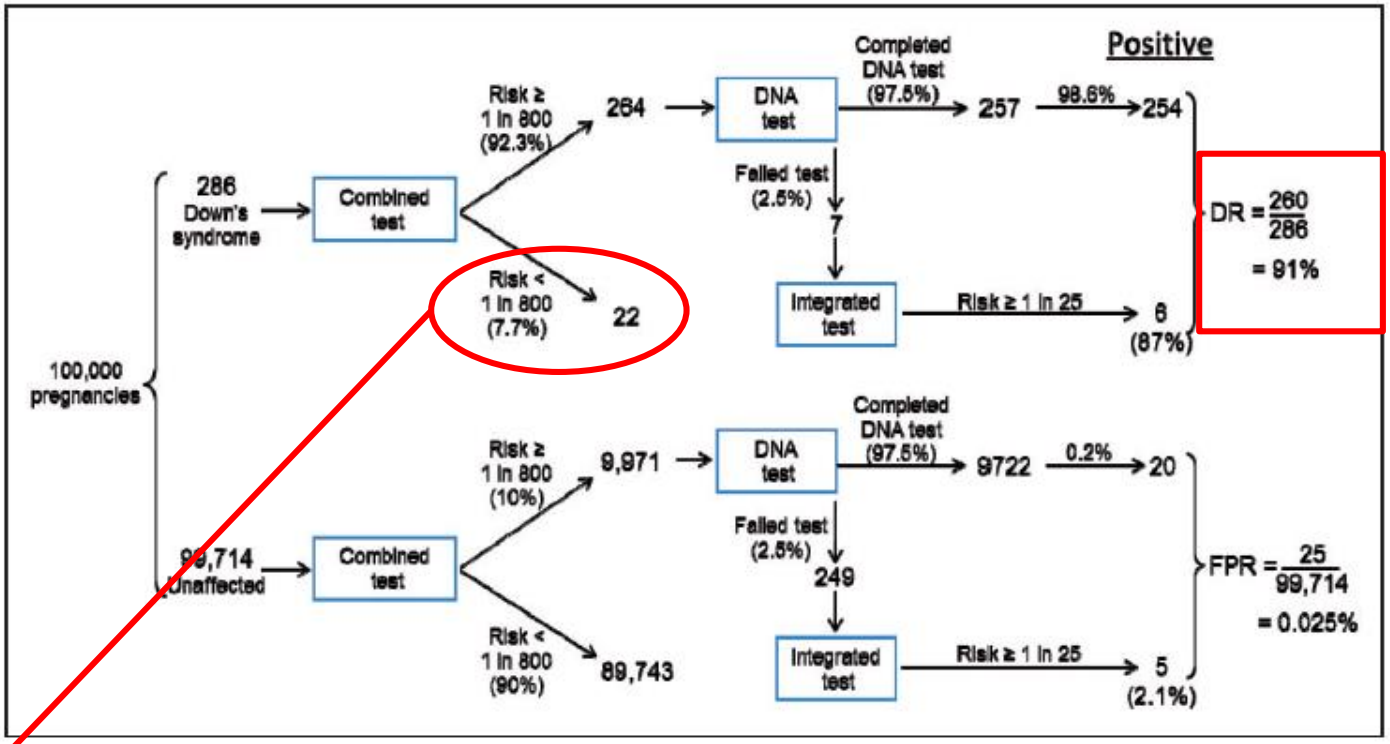
Nicholas J Wald and Jonathan P Bestwick

10% di FPR equivale a 11 settimane ad un cut-off di 1:800 circa (1:815) ed ad una DR del 92% circa



Calo al 91% della Sensibilità del DNA

Down persi

Original Article

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Nicholas J Wald and Jonathan P Bestwick

A 11 settimane

Abbassando il cut-off del test combinato
Si alzano i FP del DNA fetale

(FPR al test combinato)	Cut-off di rischio	Sensibilità (DR)	FPR dopo DNA fetale	FPR da DNA fetale da solo
10	1:815	90.8	1:4000	≅1:500
15	1:1384	92.9	1:2857	≅1:500
20	1:2075	94.2	1:2173	≅1:500
25	1:2905	95.1	1:1785	≅1:500
30	1:3885	95.8	1:1538	≅1:500

Official journal of the American College of Medical Genetics and Genomics ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

Prenatal reflex DNA screening for trisomies 21, 18, and 13

Nicholas J. Wald, FRS, FRCP[1], Wayne J. Huttly, MSc[1], Jonathan P. Bestwick, MSc[1], Robert Old, PhD[1], Joan K. Morris, PhD[1], Ray Cheng, MPhil[1], Joe Aquilina, FRCOG[2], Elisabeth Peregrine, MRCOG[3], Devender Roberts, MRCOG[4] and Zarko Alfirevic, FRCOG[4]

Table 1 Characteristics of the 22,812 pregnancies screened

Median age (years) at estimated date of delivery (IQR)	31 (28–35)
Median maternal weight (kg) (IQR)	64 (57–73)
Median gestational age (weeks + days) at blood sample (IQR)	12 + 5 (12 + 2–13 + 1)
Ethnicity	
Caucasian	11,939 (52%)
Black	1,858 (8.1%)
South Asian	6,484 (28.4%)
Oriental (East or South East Asian)	962 (4.2%)
Other	1,569 (6.9%)
Insulin-dependent diabetes	87 (0.4%)
In vitro fertilization	791 (3.5%)
Twins	381 (1.7%)
Monochorionic	80 (21%)
Dichorionic	295 (77%)
Unknown chorionicity	6 (1.6%)
Smoker	1,222 (5.4%)
Trisomy 21 (prevalence)	73 (0.32%)
Trisomy 18 (prevalence)	25 (0.11%)
Trisomy 13 (prevalence)	8 (0.04%)
All affected (prevalence)	106 (0.46%)

IQR, interquartile range.

Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

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Table 2 Performance of reflex DNA screening using a 1 in 800 combined test risk cutoff to select women for a DNA test compared with women only receiving the combined test using a 1 in 150 risk cutoff

Screening method		Affected		Unaffected[a]		
	Trisomy	Positive/total	DR (95% CI)	Positive/total	FPR (95% CI)	OAPR
Reflex DNA screening	21	69/73	95% (87–98%)	4/22,706	0.02% (0.00–0.05%)	17:1
	18	24/25	96% (80–100%)	0/22,706	0.00% (0.00–0.02%)	>24:1
	13	8/8	100% (63–100%)	0/22,706	0.00% (0.00–0.02%)	>8:1
	All	101/106	95% (89–98%)	4/22,706	0.02% (0.00–0.05%)	25:1
Combined test only	21	59/73	81% (70–89%)	532/22,706	2.34% (2.15–2.55%)	1:9
	18	20/25	80% (59–93%)	10/22,706	0.05% (0.02–0.08%)	1:2
	13	6/8	75% (35–97%)	55/22,706	0.24% (0.18–0.32%)	1:9
	All	86/106	81% (72–88%)	549/22,706	2.42% (2.22–2.62%)	1:6

CI, confidence interval; DR, detection rate; FPR, false-positive rate; OAPR, odds of being affected given a positive result.
[a]Unaffected with any of trisomy 21, 18, or 13.

Test sequenziale : una ipotesi di riflessione

- La DR del test combinato può essere portata al 95% con un tasso di FP del 25-30% e pari ad un cut-off di 1:3500 circa

- **In tal modo reclutando il 25-30% di tutta la popolazione a cui offrire il DNA fetale avremmo una DR del 95% ed un tasso di FR di 1:1500 circa**
-
- Il test sequenziale riduce di circa il 75% le AC inutili ma perde il 5% dei feti affetti

- **Il fallimento del test contribuisce a diagnosticare circa il 2% dei casi di Down**

Items for today

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- **La integrazione NT e NIPT**

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Is nuchal translucency measurement useful when cell-free DNA testing is performed?

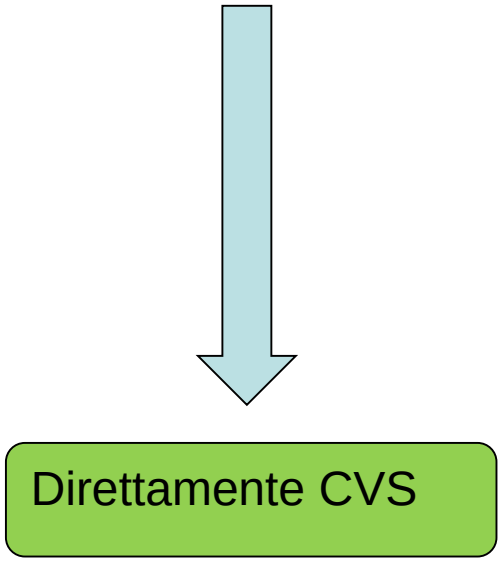
- *Lichtenbelt*: When NIPT for trisomies 13, 18, and 21 is offered to all women, NT measurement by itself has a limited added clinical value for the detection of fetal chromosomal anomalies.

- *O'Brien*: A positive NT ultrasound scan did not add to the cases of aneuploidy that were detected by cfDNA screening.

- *Langlois*: For women with a negative cfDNA screening result, NT measurement has limited clinical utility.

NT vs. cff-DNA vs. CVS

- NT non aggiunge nulla allo screening base col DNA fetale
  - Pur avendo scarsa specificità (50% circa) una NT aumentata (>95-99 centile) può essere utile ad identificare patologie rare cromosomiche, subcromosomiche e mendeliane

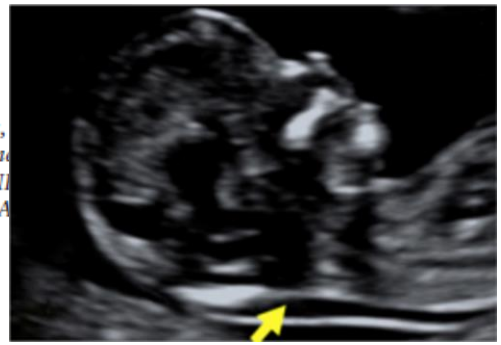


Ultrasound Obstet Gynecol 2015; **46**: 650–658
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14880

Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: a systematic review and meta-analysis

M. GRANDE*, F. A. R. JANSEN†, Y. J. BLUMENFELD‡, A. FISHER§, A. O. ODIBO¶, M. C. HAAK† and A. BORRELL*

**Department of Maternal-Fetal Medicine, Institute of Gynecology, Obstetrics and Neonatology, Hospital Clinic of Barcelona, Spain; †Leiden University Medical Center, Department of Obstetrics and Fetal Medicine, Leiden, The Netherlands; ‡Departm Obstetrics & Gynecology, Stanford University School of Medicine, Stanford, CA, USA; §Elliot Health System, Manchester, NI ¶Department of Obstetrics & Gynecology, Division of Maternal Fetal Medicine, University of South Florida, Tampa, FL, USA*



Conclusion *The use of genomic microarray provides a 5.0% incremental yield of detecting CNVs in fetuses with increased NT and normal karyotype.*

Anomalie più frequenti in NT>99° e/o 3.5 mm

- Più frequenti CNV:
- 22q.11.2 mdelez (s. di DiGeorge)
- 22q11.2 mduplicaz (iperespressione di TBX1)
- 16p11.2 mduplicaz
- 1p.36 delezione

NIPT DNA per microdelezioni

- Più frequente Mendeliana :
- S. Di Noonan

NIPT DNA per Malattie Mendeliane

medical sciences

MDPI

Article

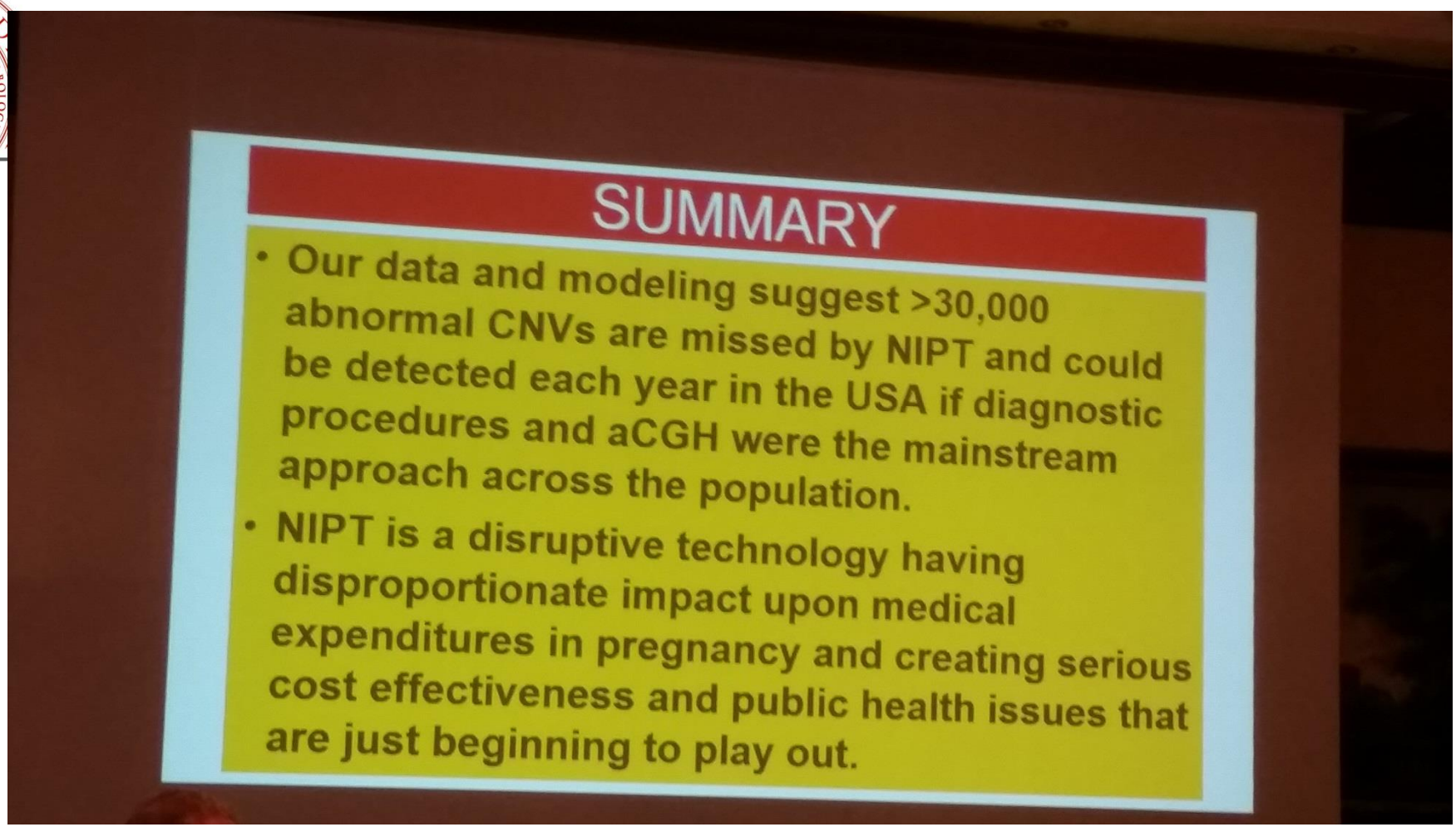
Chromosomal Microarray Analysis versus Karyotyping in Fetuses with Increased Nuchal Translucency

Rita Cicatiello [1,†], Piero Pignataro [1,†], Antonella Izzo [1], Nunzia Mollo [1], Lucia Pezone [1], Giuseppe Maria Maruotti [2], Laura Sarno [2], Gabriella Sglavo [2], Anna Conti [1,*], Rita Genesio [1,‡] and Lucio Nitsch [1,3,‡]

Table 2. Prenatal cases with chromosome anomalies not detectable by non-invasive prenatal testing (NIPT).

Chromosome Anomaly	Sample Type	Detectable by NIPT
46,XX.arr[GRCh37]16p11.2(29652999_30198600)x3 pat	AF	No
46,XY.arr[GRCh37]2p15(61529343_61564040)x1 mat,16p11.2(28833437_29046252)x3 dn	AF	No
46,XX.arr[GRCh37]22q11.2(19010936_20434800)x1 dn	CVS	No
46,XX.arr[GRCh37]1p36.23p36.33(453255_7284969)x1 dn	CVS	No
46,XX.arr[GRCh37]22q11.2(19110226_19854855)x1 dn	CVS	No
46,XY.arr[GRCh37]1q43(237335376_237418407)x1 dn	AF	No
46,XY.arr[GRCh37]1q21.1(145429097_146756493)x3 pat	AF	No
47,XX,+9	AF	No
47,XY,+mar .ish der(9)(wcp9+)mat.arr[GRCh37](1-22)x2,(X,Y)x1	CVS	No
47,XY,+mar.ish der(22)(wcp22+,TUPLE1+).arr[GRCh37]22q11.1q11.21(17374086_20088001)x3 dn	CVS	No
47,XY,+mar .ish der(9)(wcp9+).arr[GRCh37](1-22)x2,(X,Y)x1	CVS	No
mos 47,XX,+mar[8]/46,XX[8].ish i(12)(p10)(wcp12+)	CVS	No
mos 46,XX,inv(5)(p14p15)[7]/46,XX[9].arr[GRCh37]8q22.2(100072320_100155410)3 pat	CVS	No
45,XY,der(18;22)(p11?;q11?).ish der(18;22)(D18Z1+,D18S552;TUPLE1+,SHANK3+)dn.arr[GRCh37]6q16.1(95588523_95662060)x1 pat,18p11.32p11.21(146484_14117327)x1	AF	No
46,XX,add(8)(p23).ish dup(8)(p21?p23)(wcp8+)dn.arr[GRCh37]8p23.3p23.1(228758_6911631)x1,8p23.1p11.22(11858401_38964086)x3	AF	No
46,XX,der(10)t(10;12)(q26;q23).arr[GRCh37]10q26.13q26.3(123190101_135104747)x1,12q23.3q24.33 (106838149_132878426)x3	CVS	No
Short term culture: 46,XY/Long term culture: mos 45,X[4]/46,XY[12]	CVS	Not sure
mos 45,X[4]/46,XX[26]	CVS	Not sure
mos 45,X[3]/46,XX[22]	CVS	Not sure

AF: amniotic fluid; CVS: samples from chorionic villi.



Prof Mark Evans

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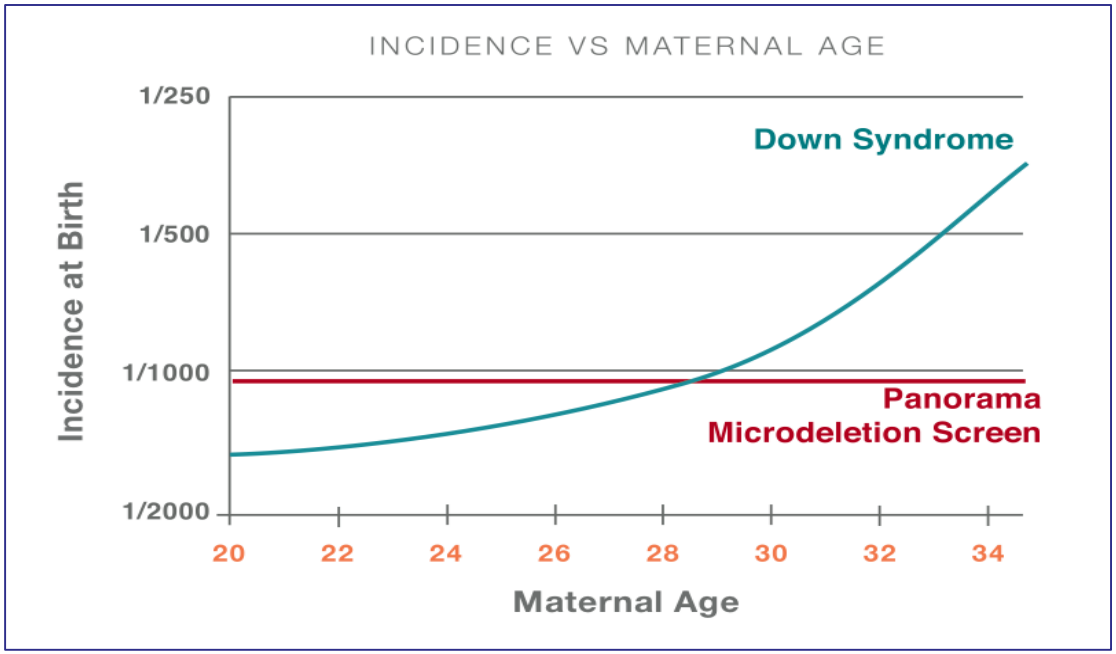
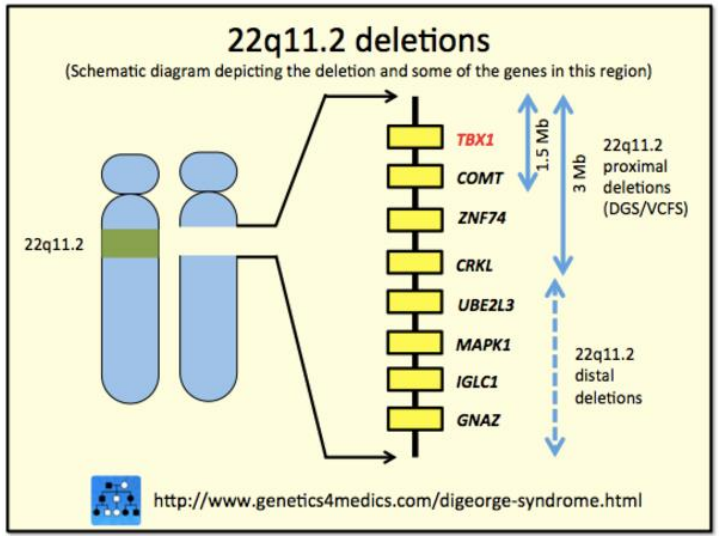
Microdelezioni



[1]Snijders, et al. *Ultrasound Obstet Gynecol 1999;13:167–170.*
[2]Combined prevalence using higher end of published ranges from Gross et. al., *Prenatal Diagnosis 2011; 39, 259-266;* and www.genetests.org.
Total prevalence may range from 1/1071 - 1/2206.

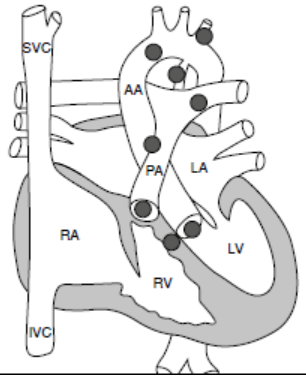
Coppia di cromosomi 22

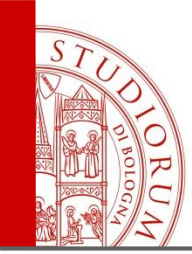
La freccia indica la delezione della regione la 22q11.2DS su uno dei due cromosomi 22.



Settori cardiaci nei difetti cardiovascolari associati

- Arco Aortico
- Arterie Polmonari
- Arterie Succlavie
- Collaterali Aorto-polmonari
- Setto Infundibolare
- Valvola Polmonare





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panorama®
natera prenatal screen

Condition	*Sensitivity (95% CI)*	*Specificity (95% CI)*	*Positive Predictive Value*	*Negative Predictive Value*
22q11.2 deletion syndrome[7,8,9]	95.7% (CI 85.5-99.5)	>99 (CI 98.6-99.9)	20%**	99.97-99.99%***
1p36 deletion syndrome[7,8]	>99% (CI 2.5-100)	>99% (CI 99.1-100)	7-17%***	99.98-99.99%***
Angelman syndrome[7,8]	95.5% (CI 77.2-99.9)	>99% (CI 99.1-100)	4%	>99.99%
Cri-du-chat syndrome[7,8]	>99% (CI 85.8-100)	>99% (CI 99.1-100)	2-5%***	>99.99%
Prader-Willi syndrome[7,8]	93.8% (CI 69.8-99.8)	>99% (CI 99.1-100)	5%	>99.99%

* Ongoing clinical follow-up is performed to ensure the NPV does not fall below the quoted value but follow up is not obtained for all low risk calls.

** PPV for 22q11.2 deletion syndrome in published studies was 20% when no ultrasound anomalies were seen and was up to 100% when ultrasound anomalies were seen prior to testing.

*** Dependent upon fetal fraction, see Panorama Risk score on report for accurrate PPV/NPV for a specific patient.

For additional information, please visit: ***www.natera.com/panorama-test/test-specs***

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MaterniT GENOME Lab Report

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Lab Director: Phillip Cacheris, MD, PhD
Tel: 877.821.7266

FINAL REPORT

Performance Characteristics

Region (associated syndrome)	Size Range (Mb)*	Median Size (Mb)*	Reportable Fetal Fraction	Estimated Sensitivity**	Estimated Specificity
Genome-wide	NA	NA	≥ 4%	96% (61–> 99%)	> 99.9%
22q11.2 (DiGeorge)	0.8–3.6	2.6	≥ 4%	> 74% (17–94%)	> 99.9%
15q11.2 (Prader-Willi & Angelman)	1.2–15.8	5.1	≥ 4%	> 59% (16–74%)	> 99.9%
11q23 (Jacobsen)	1.3–15.7	9	≥ 4%	> 87% (57–> 99%)	> 99.9%
8q24.11-q24.13 (Langer-Giedion)	7.6–8.8	7.9	≥ 4%	> 97% (80–> 99%)	> 99.9%
5p15.3 (Cri du Chat)	1.5–17.8	6	≥ 4%	> 83% (48–96%)	> 99.9%
4p16.3 (Wolf-Hirschhorn)	1.1–17.3	4.2	≥ 4%	> 73% (37–91%)	> 99.9%
1p36 (1p36 deletion syndrome)	1.6–13.3	3.8	≥ 4%	> 51% (13–81%)	> 99.9%

** Sensitivity estimated across the observed size distribution of each syndrome [per ISCA database nstd37] and across the range of fetal fractions
observed in routine clinical NIPT. Figures in parentheses indicate upper and lower estimates for sensitivity at the lowest reportable fetal fraction (4%)
and at fetal fraction ≥20%, respectively. Actual sensitivity can also be influenced by other factors such as the size of the event, total sequence counts,
amplification bias, or sequence bias.

Screening for 22q11.2 deletion syndrome by two non-invasive prenatal testing methodologies: A case with discordant results

Liang-Ming Lo [a, b], Chii-Shinn Shiau [a, b], Kuang-Chao Chen [a, b], S.W.S. Shaw [a, b, c, *], Peter Benn [d]

[a] *Department of Obstetrics and Gynecology, Taipei Chang Gung Memorial Hospital, Taipei, Taiwan*
[b] *College of Medicine, Chang Gung University, Taoyuan, Taiwan*
[c] *Prenatal Cell and Gene Therapy Group, Institute for Women's Health, University College London, London, UK*
[d] *Genetics and Genome Sciences, UCONN Health, 263 Farmington Avenue, E3050, Farmington, CT, USA*

Conclusion: Currently available NIPT for 22q11.2DS use different technologies that are not equivalent. The genome-wide counting methodology has the potential to detect deletions outside the critical 22q11.2 A–D region but current data suggests it may have a lower sensitivity for deletions within the critical region.

Test Result	Positive Loss of chromosome 22(q11.2) material

Laboratory Director's Comments
A loss of chromosome 22 material was observed. It is estimated to be 2.6 Mb in size and is suggestive of a deletion in the region 22q11.2, which is associated with DiGeorge syndrome. Genetic counseling and clinical correlation are recommended. Confirmatory testing is required if fetal confirmation and clinical interpretation of the suspected event are desired. Please refer to the "Performance" and "Limitations of the Test" sections of this laboratory report for additional information.

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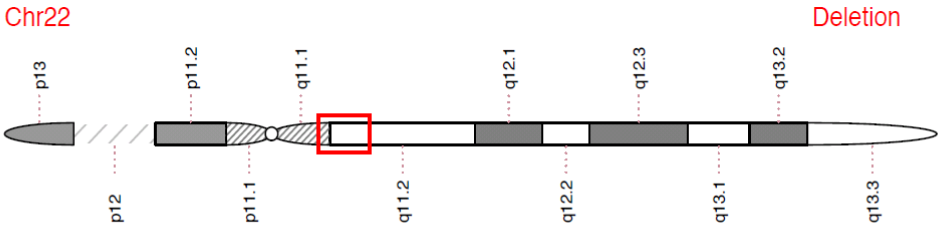


Description: An approximate 2.6 Mb loss of chromosome 22 material was observed, suggestive of a deletion in the region q11.2, associated with DiGeorge syndrome.

natera

CONCLUSIONE

ALTO RISCHIO per delezione 22q11.2 (Sindrome di DiGeorge)
Si consiglia consulenza genetica. Si segnala che l'esame svolto è un test di screening, pertanto per una diagnosi definitiva è necessario eseguire test diagnostici con metodica microarray su villi coriali o liquido amniotico.

ESITO DEL TEST

Sesso del feto: Femmina

Frazione fetale: 7,2 %

Microdelezione testata [1]	Rischio a priori [2,4]	Rischio Panorama [3]	Risultato
22q11.2 (DiGeorge)	**1/2000**	**1/19**	**Alto rischio**
1p36	1/5000	1/12400	Basso rischio
Angelman	1/12000	1/16600	Basso rischio
Cri-du-chat	1/20000	1/57100	Basso rischio
Prader-Willi	1/10000	1/13800	Basso rischio

harmony® PRENATAL TEST

Toma Il tuo futuro, oggi | Istituto di Genetica Umana dal 1979

Screening della microdelezione 22q11.2 col test Harmony

Delezione 22q11.2

	Sensibilità	Rischio di falso positivo
Interne alla regione tipica da 3Mb*	75%[3-4]	0.5%[3-4]

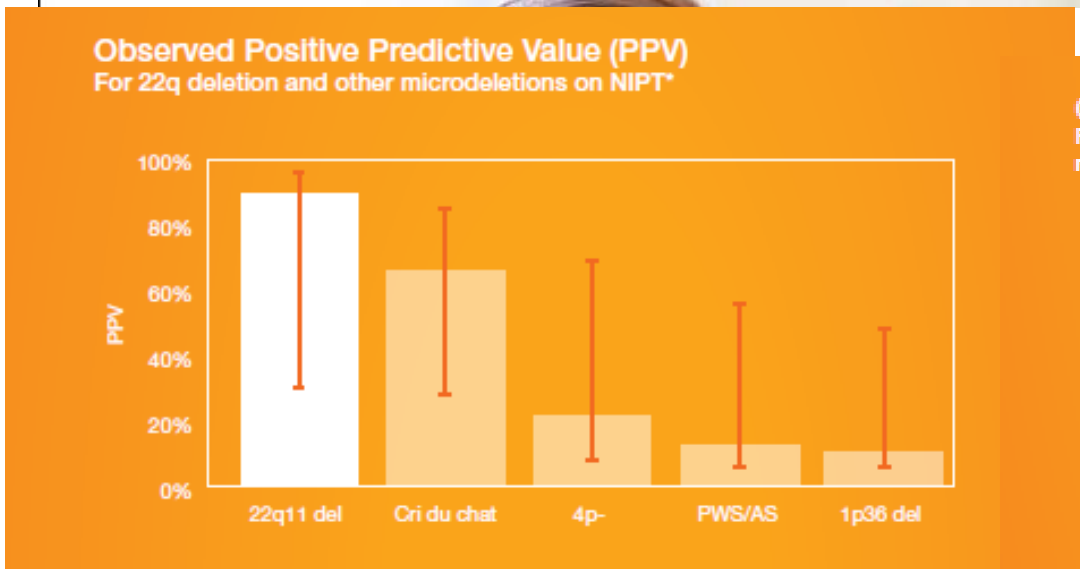
*Include anche le piccole microdelezioni atipiche localizzate internamente alla regione tipica da 3Mb

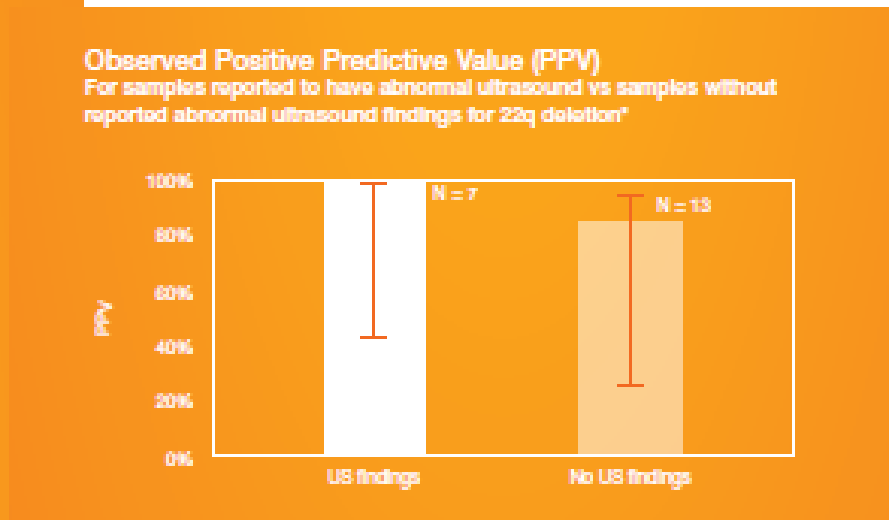
TEST NEGATIVO: il test non rileva una riduzione dei frammenti circolanti di questa regione. E' comunque utile ricordare che il test indaga il 95% delle microdelezioni che causano la sindrome 22q11 e pertanto rimane un rischio residuo, seppur estremamente ridotto, che il feto possa comunque avere la sindrome. Non è raccomandato modificare il percorso di sorveglianza ecografica e clinica di routine.

1.96 to 3.25 Mb

Verifi™ Plus Prenatal Test

An expanded NIPT panel for the additional insights you need





Manca la Sensibilità e i Falsi Positivi

Quante S. di DiGeorge ??????

Instructions For Use
REF: LPU 015-S / LPU 015

DiGeorge II (10p14) Probe

Probe Information

DiGeorge syndrome[1], and a variety of congenital malformation syndromes including Velocardiofacial syndrome (VCFS)[2], share the deletion of chromosome 22 at 22q11.2[2,3,4,5]. These chromosome 22 deletions are collectively coined CATCH22, a mnemonic that covers the clinical findings of Cardiac abnormality, Abnormal facies, Thymic aplasia, Cleft palate and Hypocalaemia/Hyperthyroidism due to a chromosome 22 deletion. In DiGeorge syndrome, however, cases have also been found in which patients have a deletion on chromosome 10p13.4 (DGS2) instead of chromosome 22[6, 7,8]. The deletion of the DGS2 locus on 10p may be 50 times less frequent than that of the DGS1 locus on 22q and has been estimated to occur in 1 in 200,000 live births[9]. A gene called BRUNOL3 (now named CELF2) has been identified within the 300kb minimally deleted region of DGS2 and is postulated to be involved in the DGS2 deletion[10]. BRUNOL3 is a candidate gene for the heart defect and thymus hypoplasia/aplasia associated with partial monosomy 10p[10] and may be involved in atrial septal defects (ASDs), a common cardiac anomaly associated with DGS2[11].

Items for today

- Test sequenziale «reflex» Test combinato + DNA fetale
- La integrazione NT e NIPT
- Confronto delle performance dello screening della Sindrome di DiGeorge
- **I pannelli per le malattie mendeliane**

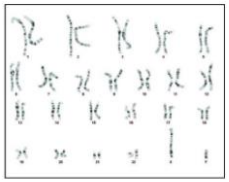
Evoluzione del NIPT: Verso le malattie mendeliane

Single Gene Mutations
NOT Detected by Routine Karyotype or Microarray

Karyotype

>7Mb Resolution

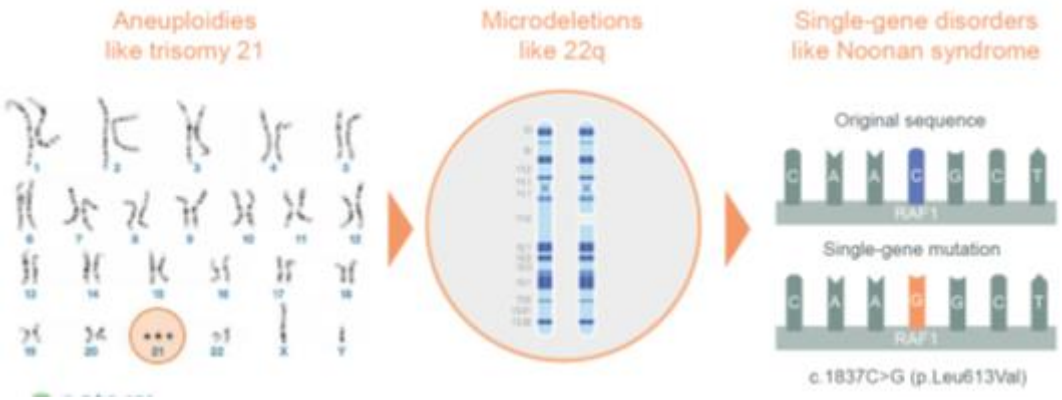
Can detect whole chromosome aneuploidy, large deletions and duplications



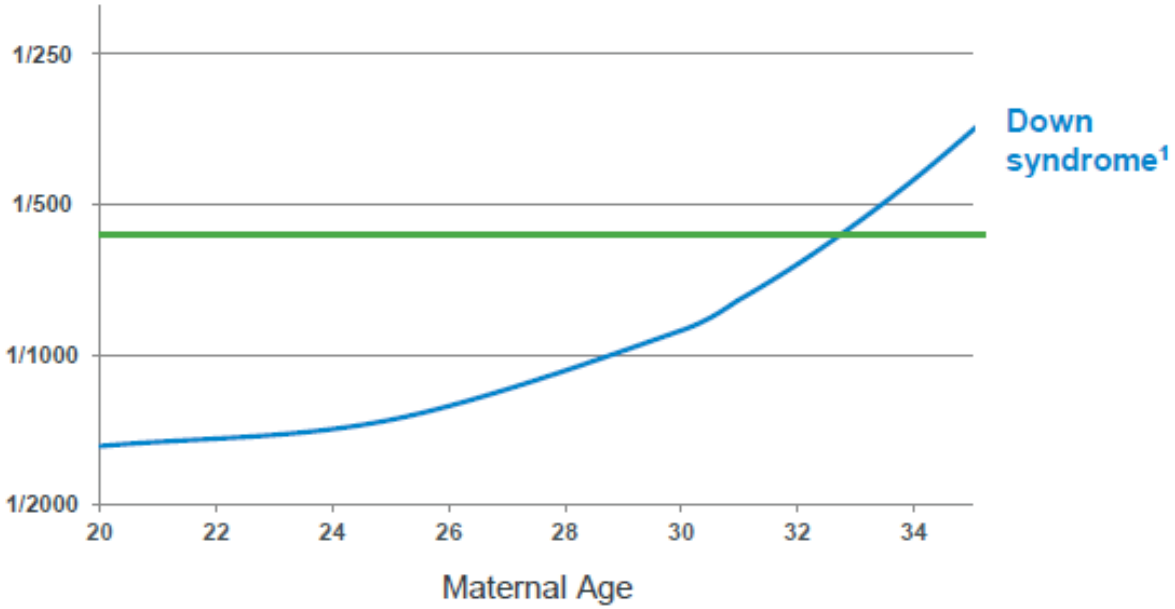
Microarray

>1Mb genome resolution, even smaller for critical regions

Can detect microdeletions and microduplications



Screening Malattie Mendeliane Dominanti de novo



Consider Vistara for the following indications:

Advanced paternal age

Women who want to know "more"

Ultrasound anomalies, such as shortened long bones and increased NT

Adjunct to CVS and amniocentesis

Compagnie che offrono Pannelli per le malattie mendeliane

- Genoma Roma (Italy) Genesafe
  - Dominanti e alcune Recessive
- Natera (USA) Vistara
  - Dominanti
- Ames Group (Italy) VeraOmnia
  - Dominanti e Recessive
- NIPT Genetics (Cipro)
  - Recessive VeraGene
  - Dominanti (in progress) VeraOmics

vistara
POINT MUTATION NIPT

Conditions screened

Syndromic Disorders	
Condition	**Gene**
Alagille Syndrome	JAG1
CHARGE syndrome	CHD7
Cornelia de Lange syndrome 1	NIPBL
Cornelia de Lange syndrome 2	SMC1A
Cornelia de Lange syndrome 3	SMC3
Cornelia de Lange syndrome 4	RAD21
Cornelia de Lange syndrome 5	HDAC8
Epileptic encephalopathy, early infantile, 2	CDKL5
Intellectual disability	SYNGAP1
Rett syndrome	MECP2
Sotos syndrome 1	NSD1
Tuberous sclerosis 1	TSC1
Tuberous sclerosis 2	TSC2

Craniosynostosis Syndromes	
Condition	**Gene**
Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis	FGFR2
Apert syndrome	
Crouzon syndrome	
Jackson-Weiss syndrome	
Pfeiffer syndrome type 1/2/3	

Skeletal Disorders	
Condition	**Gene**
Achondroplasia	FGFR2
CATSHL syndrome	
Crouzon syndrome with acanthosis nigricans	
Hypochondroplasia	
Muenke syndrome	
Thanatophoric dysplasia, type I	
Thanatophoric dysplasia, type II	
Ehlers-Danlos syndrome, classic	COL1A1
Ehlers-Danlos syndrome, type VIIA	
Osteogenesis imperfecta, type I	
Osteogenesis imperfecta, type II	
Osteogenesis imperfecta, type III	
Osteogenesis imperfecta, type IV	
Ehlers-Danlos syndrome, cardiac valvular form	COL1A2
Ehlers-Danlos syndrome, type VIIB	
Osteogenesis imperfecta, type II	
Osteogenesis imperfecta, type III	
Osteogenesis imperfecta, type IV	

Noonan Spectrum Disorders	
Condition	**Gene**
Cardiofaciocutaneous syndrome 1	BRAF
Cardiofaciocutaneous syndrome 3	MAP2K1
Cardiofaciocutaneous syndrome 4	MAP2K2
Costello syndrome / Noonan syndrome	HRAS
Noonan syndrome 1 / LEOPARD syndrome/cancers	PTPN11
Noonan syndrome 4	SOS1
Noonan syndrome 5 / LEOPARD syndrome 2	RAF1
Noonan syndrome 6 / cancers	NRAS
Noonan syndrome 8	RIT1
Noonan syndrome 9	SOS2
Noonan syndrome/cancers	KRAS
Noonan syndrome-like disorder with loose anagen hair	SHOC2
Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL)	CBL

vistara
POINT MUTATION NIPT

Disorder	Clinical actions
Osteogenesis imperfecta	• Labor and delivery management to avoid fractures • Neonatal care • Early recognition and treatment of fractures
Achondroplasia	• Labor and delivery management • Monitor for spinal stenosis • Early sleep studies to reduce probability of SIDS
Noonan syndrome	• Fetal echocardiogram • Labor and delivery management • Early assessment for learning differences
Craniosynostosis	• Fetal MRI • Avoid instrumented delivery • Corrective surgery • Early medical and behavioral interventions

GeneSafe™ DE NOVO identifies fetal conditions that could be **missed by traditional prenatal screening.**

GENE	SYNDROMIC DISORDERS
JAG1	Alagille syndrome
CHD7	CHARGE syndrome
HDAC8	Cornelia de Lange syndrome 5
NIPBL	Cornelia de Lange syndrome 1
MECP2	Rett syndrome
NSD1	Sotos syndrome 1
ASXL1	Bohring-Opitz syndrome
SETBP1	Schinzel-Giedion syndrome
SIX3	Holoprosencephaly
	NOONAN SYNDROMES
BRAF	Cardiofaciocutaneous syndrome 1
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL)
KRAS	Noonan syndrome/cancers
MAP2K1	Cardiofaciocutaneous syndrome 3
MAP2K2	Cardiofaciocutaneous syndrome 4
NRAS	Noonan syndrome 6/cancers
PTPN11	Noonan syndrome 1/ LEOPARD syndrome/cancers
PTPN11	Juvenile myelomonocytic leukemia (JMML)
RAF1	Noonan syndrome 5/LEOPARD syndrome 2
RIT1	Noonan syndrome 8
SHOC2	Noonan syndrome-like disorder with loose anagen hair
SOS1	Noonan syndrome 4

GENE	SKELETAL DISORDERS
COL2A1	Achondrogenesis, type II or hypochondrogenesis
FGFR3	Achondroplasia
	CATSHL syndrome
	Crouzon syndrome with acanthosis nigricans
	Hypochondroplasia
	Muenke syndrome
	Thanatophoric dysplasia, type I
	Thanatophoric dysplasia, type II
COL1A1	Ehlers-Danlos syndrome, classic
	Ehlers-Danlos syndrome, type VIIA
	Osteogenesis imperfecta, type I
	Osteogenesis imperfecta, type II
	Osteogenesis imperfecta, type III
	Osteogenesis imperfecta, type IV
COL1A2	Ehlers-Danlos syndrome, cardiac valvular form
	Ehlers-Danlos syndrome, type VIIB
	Osteogenesis imperfecta, type II
	Osteogenesis imperfecta, type III
	Osteogenesis imperfecta, type IV
	CRANIOSYNOSTOSIS SYNDROMES
FGFR2	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis
	Apert syndrome
	Crouzon syndrome
	Jackson-Weiss syndrome
	Pfeiffer syndrome type 1
	Pfeiffer syndrome type 2
	Pfeiffer syndrome type 3

GeneSafe™ detects de novo mutations in 25 genes causing 44 different genetic disorders. The genetic conditions screened by this innovative test often occur in the absence of a family history of the condition. This is a paradigm shift in prenatal screening. GeneSafe™ screens for de novo mutations that cannot be detected by standard carrier screening, as these mutations are not present on the parents. The genetic disorders screened by GeneSafe™ can cause **skeletal dysplasias, cardiac defects,** [1-2-3] **multiple congenital anomalies,** [4-5] **autism,** [6] **epilepsy** [7] **and/or intellectual disability.** [8-9]

AMES Group
GENETICA MEDICA · MICROBIOLOGIA · PATOLOGIA CLINICA

Vera omnia

Sindrome di Costello	HRAS
Sindrome di Tay-Sachs	HEXA
Sindrome di PKAN	PANK2
Sindrome della Tripla-H	SLC25A1
Sindrome di Coffin-Lowry	RPS6KA3
Sindrome di Alagille	JAG1

Patologie scheletriche	GENE
Acondrogenosi tipo 2	COL2A1
Acondroplasia Sindrome CATSHL Sindrome di Crouzon con acanthosis nigricans Ipocondroplasia Sindrome di Muenke Displasia tanatafora, tipo I Displasia tanatafora, tipo II	FGFR3
Sindrome di Ehlers - Danlos, classica Sindrome di Ehlers - Danlos, tipo VIIA Osteogenesi imperfetta, tipo I Osteogenesi imperfetta, tipo II Osteogenesi imperfetta, tipo III Osteogenesi imperfetta, tipo IV	COL1A1
Sindrome di Ehlers - Danlos, forma cardiaco - valvolare Sindrome di Ehlers - Danlos, tipo VIIB Osteogenesi imperfetta, tipo II Osteogenesi imperfetta, tipo III Osteogenesi imperfetta, tipo IV	COL1A2

Sindrome di Noonan	GENE
Sindrome Cardio facio cutanea (CFS) tipo 1	BRAF
Sindrome di Noonan - simile con o senza leucemia mielomonocitica giovanile	CBL
Sindrome di Noonan /cancers	KRAS
Sindrome Cardio facio cutanea (CFS) tipo e 3	MAP2K1
Sindrome Cardio facio cutanea (CFS) tipo 4	MAP2K2
Sindrome di Noonan 6/cancers	NRAS
Sindrome di Noonan 1/Sindrome di LEOPARD/cancers	PTPN11
Leucemia mielomonocitica giovanile (JMML)	PTPN11
Sindrome di Noonan 5/Sindrome di LEOPARD 2	RAF1
Sindrome di Noonan 8	RIT1
Sindrome Noonan - simile con capelli caduchi in fase anagen	SHOC2
Sindrome di Noonan 4	SOS1

Craniosinostosi	GENE
Sindrome di Antley - Bixler senza anomalie genitali o disordini della steroidognesi Sindrome di Apert Sindrome di Crouzon Sindromedi Jackson - Weiss Sindrome di Pfeiffer, tipo 1 Sindrome di Pfeiffer, tipo 2 Sindrome di Pfeiffer, tipo 3	FGFR2

VERAomics

NIPD GENETICS

Table 2. List of conditions to be targeted on "VERAomics" test. AD, autosomal dominat; AR, autosomal recessive; XLD, X-linked dominant.

Condition	Gene	Mode of Inheritance
Achondroplasia	*FGFR3*	AD
Alagille syndrome	*JAG1*	AD
Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis	*FGFR2*	AD
Apert syndrome	*FGFR2*	AD
Cardiofaciocutaneous syndrome 1	*BRAF*	AD
Cardiofaciocutaneous syndrome 3	*MAP2K1*	AD
CATSHL syndrome	*FGFR3*	AD
CHARGE syndrome	*CHD7*	AD
Cornelia de Lange syndrome 1	*NIPBL*	AD
Cornelia de Lange syndrome 3	*SMC3*	AD
Cornelia de Lange syndrome 4	*RAD21*	AD
Costello syndrome/Noonan syndrome	*HRAS*	AD
Crouzon syndrome	*FGFR2*	AD
Crouzon syndrome with acanthosis nigricans	*FGFR3*	AD
Ehlers-Danlos syndrome, classic	*COL1A1*	AD
Ehlers-Danlos syndrome, type VIIA	*COL1A1*	AD
Ehlers-Danlos syndrome, type VIIB	*COL1A2*	AD
Hypochondroplasia	*FGFR3*	AD
Intellectual disability	*SYNGAP1*	AD
Jackson-Weiss syndrome	*FGFR2*	AD
Muenke syndrome	*FGFR3*	AD
Noonan syndrome	*KRAS*	AD
Noonan syndrome 1/LEOPARD syndrome	*PTPN11*	AD
Noonan syndrome 4	*SOS1*	AD
Noonan syndrome 5/LEOPARD syndrome 2	*RAF1*	AD
Noonan syndrome 6/cancers	*NRAS*	AD
Noonan syndrome 8	*RIT1*	AD
Noonan syndrome 9	*SOS2*	AD
Noonan syndrome-like disorder with loose anagen hair	*SHOC2*	AD
Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL)	*CBL*	AD
Osteogenesis imperfecta, type I	*COL1A1*	AD
Osteogenesis imperfecta, type II	*COL1A1*	AD
Osteogenesis imperfecta, type II	*COL1A2*	AD
Osteogenesis imperfecta, type III	*COL1A1*	AD
Osteogenesis imperfecta, type III	*COL1A2*	AD
Osteogenesis imperfecta, type IV	*COL1A1*	AD
Osteogenesis imperfecta, type IV	*COL1A2*	AD
Pfeiffer syndrome type 1/2/3	*FGFR2*	AD
Sotos syndrome 1	*NSD1*	AD
Thanatophoric dysplasia, type I	*FGFR3*	AD
Thanatophoric dysplasia, type II	*FGFR3*	AD
Tuberous sclerosis 1	*TSC1*	AD
Tuberous sclerosis 2	*TSC2*	AD

Pannelli per le malattie Mendeliane recessive

GeneSafe™ INHERITED

allows detection of common inherited genetic disorders in the fetus

GENE	GENETIC DISORDER
CFTR	Cystic Fibrosis
CX26 (GJB2)	Deafness autosomal recessive type 1A
CX30 (GJB6)	Deafness autosomal recessive type 1B
HBB	Thalassemia-Beta
HBB	Sickle cell anemia

Malattie ad elevata incidenza rilevate con Vera Omnia®	GENE
Fibrosi Cistica	CFTR
Sordità ereditaria tipo 1A	CX26 (GJB2)
Sordità ereditaria tipo 1B	CX30 (GJB6)
Beta Talassemia	HBB
Anemia falciforme	HBB
Fenilchetonuria	PAH

Malattie a bassa incidenza e/o ad insorgenza *DE NOVO*	GENE
Malattie Sindromiche	GENE
Sindrome di Gaucher	GBA
Sindrome Dubowitz	LIG4-NSUN2
Sindrome di Richner-Hanhart	TAT
Sindrome di Sjögren-Larsson	ALDH3A2

VERAgene
comprehensive NIPT

Table 1. Summary of the 50 monogenic disorders targeted on VERAgene.

Condition	Gene	# of mutations targeted
Abetalipoproteinemia	*MTTP*	1
Arthrogryposis, mental retardation seizures	*SLC35A3*	1
Autosomal recessive polycystic kidney disease	*PKHD1*	30
Bardet Biedl syndrome 12	*BBS12*	4
Beta thalassemia	*HBB*	88
Canavan disease	*ASPA*	4
Choreacanthocytosis	*VPS13A*	1
Crigler Najjar syndrome, Type I	*UGT1A1*	10
Cystic fibrosis	*CFTR*	122
Factor V Leiden thrombophilia	*F5*	1
Factor XI deficiency	*F11*	4
Familial dysautonomia	*IKBKAP*	3
Familial Mediterranean fever	*MEFV*	8
Fanconi anemia (FANCG-related)	*FANCG*	3
Glycine encephalopathy (GLDC-related)	*GLDC*	2
Glycogen storage disease, Type 3	*AGL*	14
Glycogen storage disease, Type 7	*PFKM*	3
GRACILE syndrome	*BCS1L*	12
Inclusion body myopathy, type 2	*GNE*	2
Isovaleric acidemia	*IVD*	1
Joubert syndrome, type 2	*TMEM216*	2
Junctional epidermolysis bullosa, Herlitz type	*LAMC2*	1
Leber congenital amaurosis (LCA5-related)	*LCA5*	3
Leydig cell hypoplasia [Luteinizing hormone resistance]	*LHCGR*	10
Limb girdle muscular dystrophy, type 2E	*SGCB*	6
Lipoamide dehydrogenase deficiency [Maple syrup urine disease, type 3]	*DLD*	7
Lipoprotein lipase deficiency	*LPL*	1
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	*HADHA*	2
Maple syrup urine disease, type 1B	*BCKDHB*	5

NIPD GENETICS

https://www.nipd.com/veragene/

Panelli avanzati mendeliani

- Mancanza di informazioni chiare sulle performance
- Mancanza di indicazioni cliniche specifiche
- Forse la prima proposta : Malattie recessive in genitori carrier e/o in aree geografiche a rischio aumentato
- Panelli per malattie dominanti de novo prima dell'ecografia del 2 trimestre
-

Conclusioni

- Quadro in rapida evoluzione
- Competenza di genetica clinica e molecolare
- Alta aspettativa delle pazienti (spesso inaccettabile la performance del test combinato)
- Offerta «privata» deve essere «provata» da pubblicazioni su casistiche prospettiche
- La diagnosi invasiva del futuro ha un nuovo ruolo molto più mirato e di alta competenza