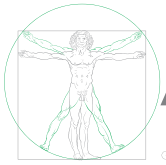

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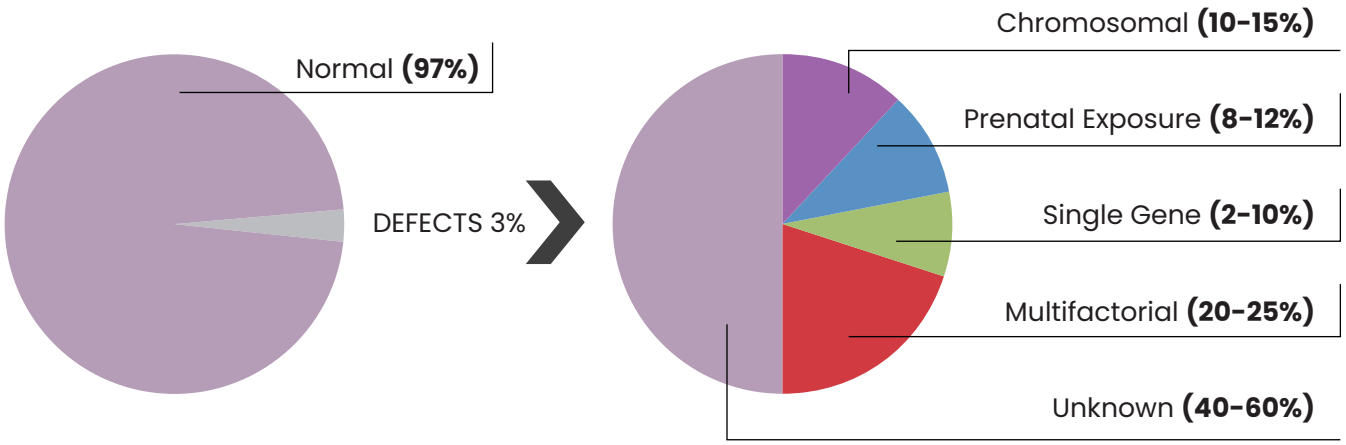
I DIFETTI CONGENITI (DC)

- **Alterazioni dello sviluppo umano** che **si verificano al momento del concepimento o durante la gravidanza** determinano problemi nello sviluppo corporeo o nel funzionamento di organi.

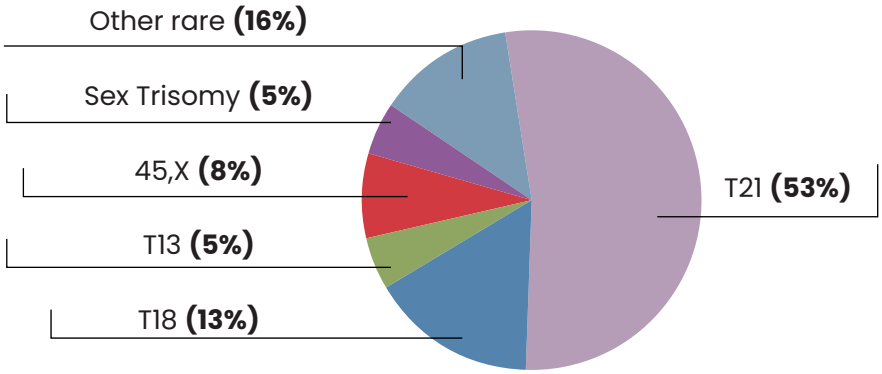
- La frequenza complessiva intorno al **5-6% dei nati.**

- **8 milioni di bambini nel mondo ogni anno**, oltre 25.000 in Italia.

- **Prime cause di morte al di sotto dei 5 anni di vita.**



Adapted from Stevenson, RE and Hall, J. Human Malformations and Related Anomalies, 2nd ed. 2006



Data adapted from Wellesley. D, et al., Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe. Eur J of Hum Gen, 11 January 2012

Conventional Prenatal Screening Options

Detection Rates for Trisomy 21

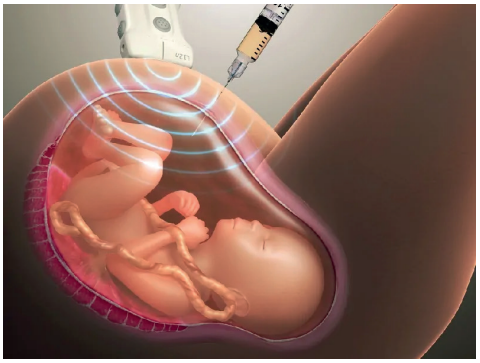
		Detection Rate (%)
1st Trimester	NT Ultrasound	64 - 70
1st Trimester	1st Trimester Blood Screen | NT Ultrasound	82 - 87
2st Trimester	Triple Screen	69
2st Trimester	Quadruple Screen	81
Integrated Screen	1st Trimester Blood Screen | NT Ultrasound | 2st Trimester Blood Screen	94 - 96
Serum Integrated	1st Trimester Blood Screen | 2st Trimester Blood Screen	85 - 88

False Positive Rate: 5%

ACOG Practice Bulletin No. 77, January 2007

Actual detection rates and false positive rates will vary slightly based on the laboratory used.

Invasive Prenatal Testing



- **Gold-standard diagnostic tests**
  - Chorionic Villus Sampling (CVS) at 10-13 weeks
  - Amniocentesis at 15-20 weeks
- **Present risk to patient and fetus**
  - 0.4% risk of miscarriage with amniocentesis
  - Risk of maternal bleeding, infection, leaking

Non-Invasive Prenatal Testing NIPT

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L'UTILIZZO DEL NIPT

TABLE 2. Conditions for Which Cell-free DNA Testing Is Clinically Available.*

- **Common autosomal aneuploidies**

Trisomy 21
Trisomy 18
Trisomy 13

- **Sex chromosome aneuploidies**

45, X
47, XXX
47, XXY
47, XYY

- **Rate autosomal aneuploidies**

Whole-chromosome aneuploidy of any autosome (trisomy 7, 15, 16, and 22 are the most commonly detected)

- **Microdeletion and microduplication syndromes**

1p36 deletion
Wolf-Hirschhorn syndrome (terminal 4p deletion)
Cri du chat syndrome (terminal 5p deletion)
Langer-Giedion syndrome (8q24 deletion)
Jacobsen's syndrome (terminal 11q deletion)
Prader-Willi and Angelman syndromes (15q11.2-q13 deletion)
DiGeorge syndrome (22q11.2 deletion)

- **Copy-number variants larger than 7Mb**

- **Triploidy**

** The sex of the fetus is also reported if the patient request it, but not in all countries.*

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FALSI POSITIVI

TABLE 3. Reported Biologic Causes of False Positive and False Negative Cell-free DNA Results.*

- **Caused of false positive results**

Confined placental mosaicism (placenta aneuploid, fetus euploid)

True fetal mosaicism

Death of a twin in utero

Maternal incidental findings
- Copy-number variant
- Chromosome abnormality
- 45, X or 47, XXX
- Mosaic trisomy for an autosome
- Leiomyoma

Cancer
- Hodhkin's or non-Hodgkin's lymphoma (most common)
- Other lymphomas (follicular, cutaneous T cell)
- Breast cancer
- Colorectal cancer
- Chronic myelogenous leukemia
- Multiple myeloma
- Other cancers (neuroendocrine, angiosarcoma, small-cell carcinoma)

Previous organ or bone marrow transplant from male donor

Medical condition or treatment affecting quality of circulating DNA
- Autoimmune disease
- B_{12} deficiency
- Intrahepatic cholestasis of pregnancy

FALSI NEGATIVI

TABLE 3. Reported Biologic Causes of False Positive and False Negative Cell-free DNA Results.*

- **Caused of false negative results**

Low fetal fraction
- Maternal obesity
- Multiple gestation causing low fetal fractionper fetus
- Maternal medical condition or treatment affecting quality of circulating DNA
- Certain fetal chromosomal aneuploidies (e.g., triploidy)

Confined placental mosaicism (placenta euploid, fetus aneuploid, or mosaic)

** Falce positive results are much more common than false negative results (88% vs. 12%).*

Bianchi DW N Engl J Med. 2018 ;379(5):464-473.

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Multisite assessment of the impact of cell-free DNA-based screening for rare autosomal aneuploidies on pregnancy management and outcomes

Tamara Mossfield[1*†], Erica Soster[2†], Melody Menezes[3], Gloudi Agenbag[4], Marie-Line Dubois[5], Jean Gekas[6], Tristan Hardy[3], Monika Jurkowska[7], Pascale Kleinfinger[8], Kelly Loggenberg[4], Pablo Marchili[9] and Roberto Sirica[10] on behalf of the Global Expanded NIPT Consortium[‡]

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Cell-free (cf) DNA screening is a noninvasive prenatal screening approach that is typically used to screen for common fetal trisomies, with optional screening for sex chromosomal aneuploidies and fetal sex. Genome-wide cfDNA screening can screen for a wide variety of additional anomalies, including rare autosomal aneuploidies (RAAs) and copy number variants. Here, we describe a multi-cohort, global retrospective study that looked at the clinical outcomes of cases with a high-risk cfDNA screening result for a RAA. Our study cohort included a total of 109 cases from five different sites, with diagnostic outcome information available for 68% (74/109) of patients. Based on confirmatory diagnostic testing, we found a concordance rate of 20.3% for presence of a RAA (15/74) in our study population. Pregnancy outcome was also available for 77% (84/109) of cases in our cohort. Many of the patients experienced adverse pregnancy outcomes, including intrauterine fetal demise, fetal growth restriction, and preterm birth. These adverse outcomes were observed both in patients with fetal or placental confirmation of the presence of a RAA, as well as patients that did not undergo fetal and/or placental diagnostic testing. In addition, we have proposed some suggestions for pregnancy management and counseling considerations for situations where a RAA is noted on a cfDNA screen. In conclusion, our study has shown that genome-wide cfDNA screening for the presence of rare autosomal aneuploidies can be beneficial for both patients and their healthcare practitioners. This can provide a possible explanation for an adverse pregnancy outcome or result in a change in pregnancy management, such as increased monitoring for adverse outcomes.

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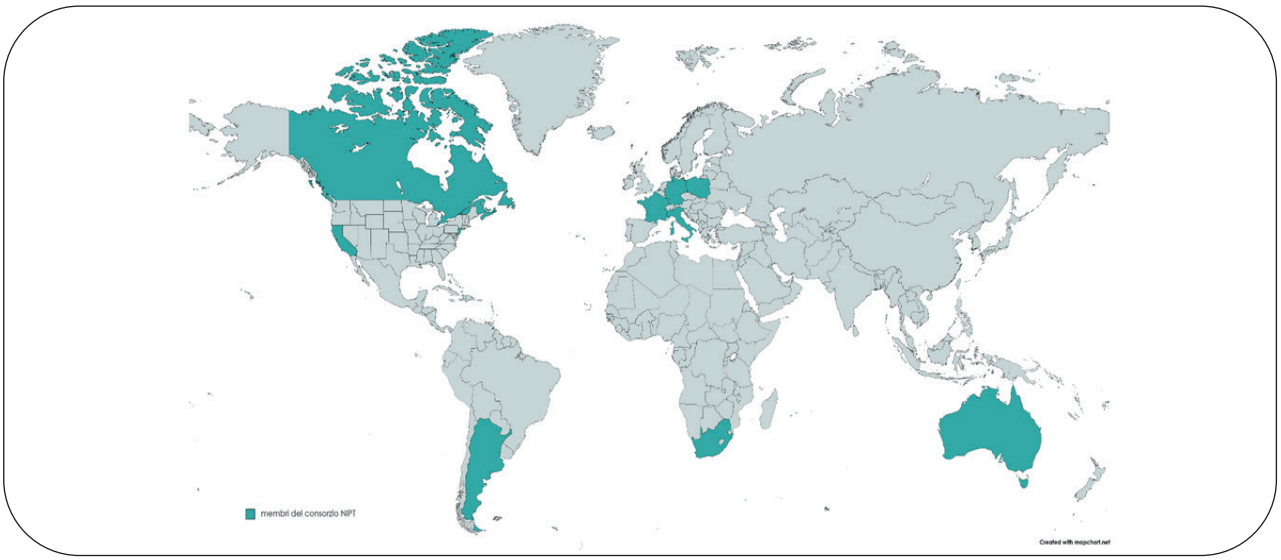
11 ISTITUTI DA **9 DIFFERENTI** PAESI FACENTI PARTE DEL **CONSORZIO NIPT**



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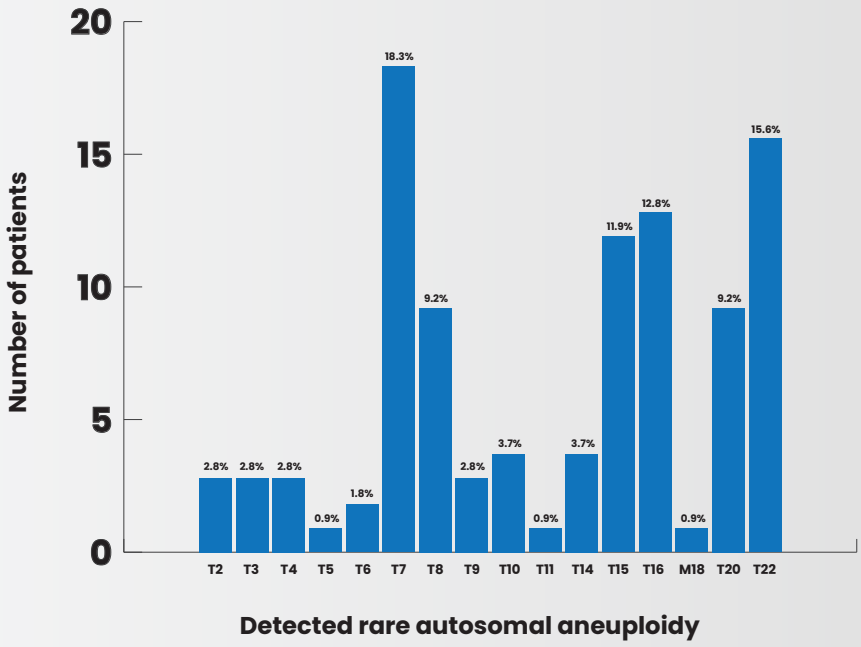

FIGURE 1
Detected rare autosomal aneuploidies in the study cohort. There were no rare autosomal aneuploidies observed on chromosomes 1, 12, 17, or 19; trisomies observed on chromosomes 13, 18, or 21 were not included.

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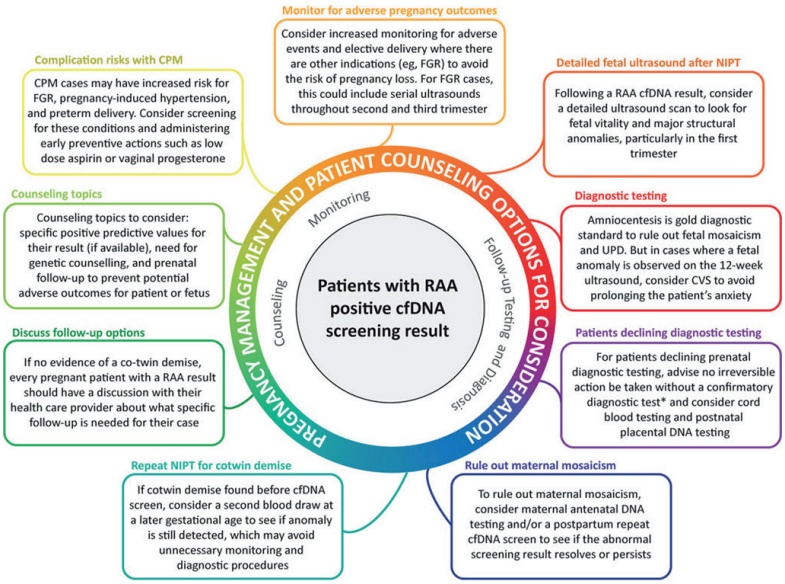
Observed concordance	Case no.	cfDNA screening result	Fetal fraction (%)	Interventions prompted	Pregnancy outcome	Pregnancy complications	Newborn physical exam
Fetus (mosaic)	1	Trisomy 7	13	TOP	Elective TOP	—	—
Fetus (mosaic)	2	Trisomy 10	N/a	TOP	Elective TOP	—	—
Fetus	3	Trisomy 14	N/a	Fetal anatomy scan	IUFD	—	—
Fetus (mosaic/UPD)	4	Trisomy 15	N/a	TOP	Elective TOP	—	—
Fetus (mosaic)	5	Trisomy 16	5	TOP	Elective TOP	—	—
Fetus (UPD)	6	Trisomy 16	9	Alteration of pregnancy monitoring[a]	Liveborn[b]	Preeclampsia	FGR, prematurity, cleft palate
Fetus (mosaic)	7	Trisomy 16	N/a	Alteration of pregnancy monitoring[a]	Unknown (lost to follow-up)	Unknown	Unknown
Fetus (mosaic)	8	Trisomy 16	9	Alteration of pregnancy monitoring[a]	Unknown (lost to follow-up)	Unknown	Unknown
Fetus (mosaic)	9	Trisomy 20	N/a	Alteration of pregnancy monitoring[a]	Liveborn[c]	None	Normal. Baby required breathing support at birth but was otherwise well
Fetus	10	Trisomy 22	N/a	Other	IUFD	—	—
Placenta (mosaic)	11	Trisomy 8	N/a	Alteration of pregnancy monitoring[a]	Liveborn[d]	Severe FGR	Normal
Placenta (mosaic)	12	Trisomy 10	N/a	Alteration of pregnancy monitoring[a]	Unknown (lost to follow-up)	Unknown	Unknown
Placenta	13	Trisomy 15	N/a	Alteration of pregnancy monitoring[a]	Elective TOP	Severe FGR	Hypospadias
Placenta (mosaic)	14	Trisomy 16	N/a	Alteration of pregnancy monitoring[a]	Liveborn[e]	Preeclampsia	No information provided
Placenta (mosaic)	15	Trisomy 16	10	—	Liveborn[f]	None	No information provided

CONFERMATI **15/109 (13%)**

10 fetali
5 placentari
9 alterazioni a mosaico
2 UPD

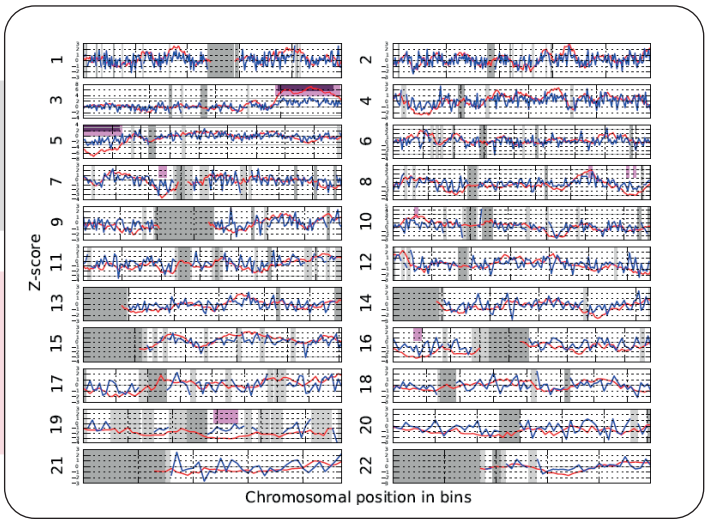


Casi clinici Vera Plus Prenatal Test
Aneuploidie di tutti i cromosomi autosomici più macrodelezioni e macroduplicazioni > 7 Mb

CASO CLINICO 1:
il Vera Prenatal Test PLUS rileva una duplicazione parziale del cromosoma 3 ed una delezione parziale del cromosoma 5

La gestante di 20 anni si sottopone al **Vera Prenatal Test Plus** a 11 sett. di gravidanza.

Vera Prenatal Test PLUS mostra una duplicazione di parte del cromosoma 3 e una delezione di parte del cromosoma 5.



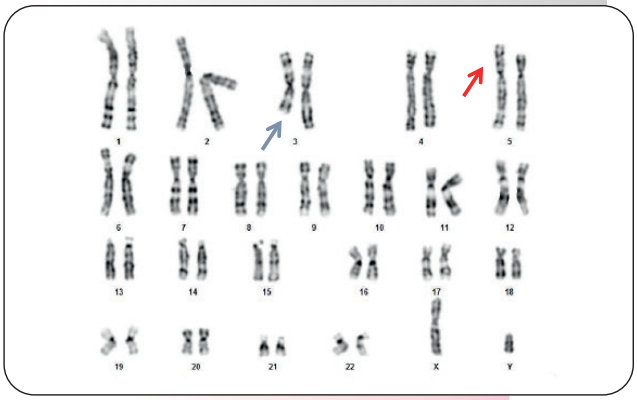
La gestante si sottopone ad **amniocentesi:** Cariotipo femminile con una variante strutturale a carico di uno dei cromosomi della coppia 5.
Si consiglia consulenza genetica e cariotipo dei genitori del probando.

Il cariotipo paterno mostra una traslocazione apparentemente bilanciata tra il braccio lungo di un cromosoma della coppia 3 ed il braccio corto di un cromosoma della coppia 5.

Cariotipo da liquido amniotico

46, XX, der(5)pat

Cariotipo Paterno da sangue periferico



46, XY, t(3;5)(q24;p15)mat

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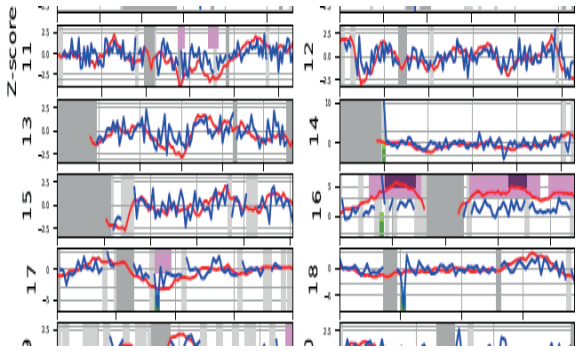
CASO CLINICO 2:
il Vera Prenatal Test Plus rileva una trisomia del cromosoma 16

La gestante di 31 anni si sottopone al **Vera Prenatal Test Plus** a 11 sett. di gravidanza.

Vera Prenatal test PLUS rileva una trisomia del cromosoma 16



La gestante si sottopone a **villocentesi** presso l'Azienda Ospedaliera Universitaria Città della salute e della scienza di Torino.
Il risultato conferma una duplicazione dell'intero cromosoma 16.
Tuttavia la gravidanza procede senza problemi e non vengono riscontrate alterazioni all'ecografia.

Risultato:
Qualità dell'esperimento array-CGH: Ottimo
Codice array: 252192442864_1_2 (Griglia di analisi 021924_D_F_20101001

L'analisi eseguita il DNA fetale estratto da un campione di villi coriali della Signora ****** ha evidenziato una duplicazione dell'intero cromosoma 16.

Il risultato, secondo l'attuale nomenclatura, è riportato come segue:
arr[GRCh37] 16p13.3q24.3(106271_90111263)x3
arr[GRCh37](X)x2

La contaminazione del DNA fetale da parte di quello materno è stata esclusa attraverso l'analisi di 15 marcatori polimorfici (PowerPlex® 16 HS System, Promega).

La gestante si sottopone ad Amniocentesi: viene riscontrato un mosaicismo del cromosoma 16. 47,XX,+16[3]/46,XX[15]

Risultato:
47,XX,+16[3]/46,XX[15]

Osservazioni

Cariotipo femminile con due linee cellulari:
- La prima (3 colonie da 3 colture) a 47 cromosomi con trisomia 16;
- La seconda (15 colonie da 3 colture) con cariotipo normale (46,XX).

Si consiglia consulenza genetica.

Follow-up
La gestante si sottopone a consulenza genetica ed esegue ecografia a 20+3 che evidenziano valori biometrici fetali al 10° centile per estremo cefalico e circonferenza addominale, <5° per ossa lunghe.
La coppia decide di portare avanti la gravidanza.

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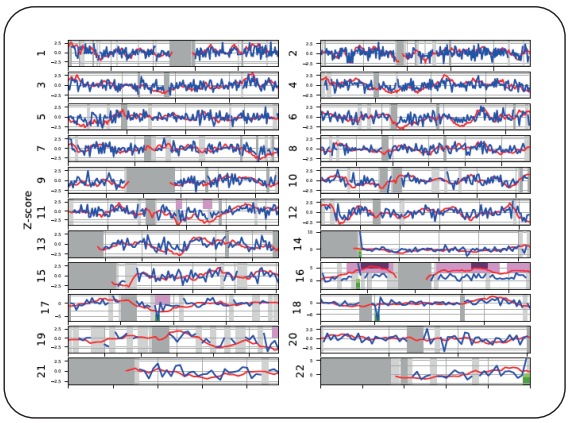
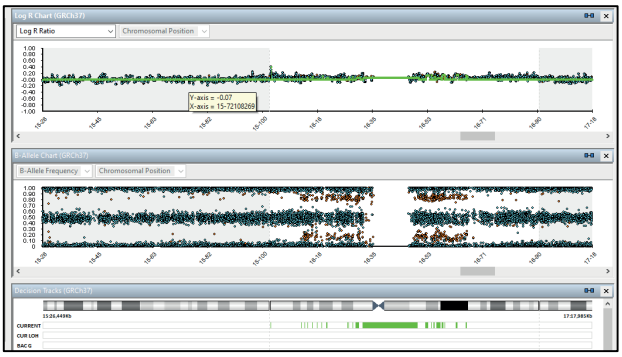
CASO CLINICO 3:
il Vera Prenatal Test Plus rileva una trisomia del cromosoma 16

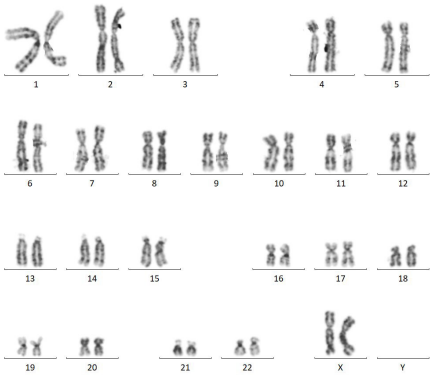


Presenza di una duplicazione, a mosaico, con un'estensione di circa 55 Mbp, presente a livello della citobanda p13.13-q21 sul cromosoma 16.

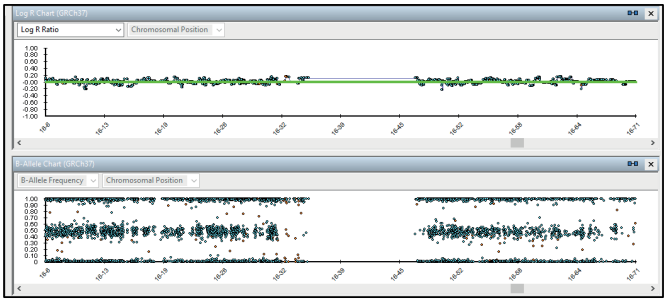
1
SNP-ARRAY SU LIQUIDO AMNIOTICO



2
CARIOTIPO



3
SNP-Array da cellule tripsinizzate
arr(1-22,X)x2



- Mosaicismo confinato alla placenta?
- Possibile contaminazione del liquido amniotico?

LINEE GUIDA SIEOG Edizione 2015

E' opportuno eliminare la prima parte del campione (0,5-1 ml) che potrebbe contenere cellule non fetali e falsare l'interpretazione dei risultati (Livello di raccomandazione B).
Si effettua quindi il prelievo di una quantità di liquido amniotico corrispondente in millilitri alle settimane di gravidanza e comunque non eccedente 20 ml (Livello di raccomandazione B).

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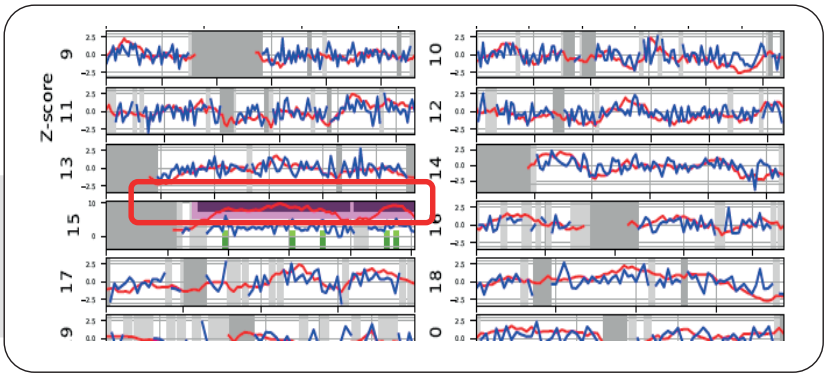
CASO CLINICO 4:
il Vera Prenatal Test Plus rileva una trisomia del cromosoma 15

La gestante di 37 anni si presenta a 15 sett. di gravidanza.

Vera Prenatal Test PLUS
positivo per trisomia del cromosoma 15.



La gravidanza procede regolarmente senza riscontri ecografici di anomalie.
La coppia decide, dopo consulenza genetica, di sottoporsi ad amniocentesi che viene eseguita presso l'Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino.

L'esame sul campione di liquido amniotico mostra la presenza di assetto trisomico a mosaico di basso grado del cromosoma 15, inoltre, l'analisi di segregazione del cromosoma 15 mostra la presenza di disomia uniparentale materna.

ESAMI GENETICI ESEGUITI SUL CAMPIONE DI LIQUIDO AMNIOTICO

- Test rapido (QF-PCR) per aneuploidie dei cromosomi 13, 18, 21 e pannello aggiuntivo per i cromosomi 15, 16 e 22: **presenza di assetto trisomico a mosaico di basso grado del cromosoma 15;**
- Esame del cariotipo fetale: 46,XY [cariotipo maschile normale in tutte e 24 le colonie esaminate];
- Analisi di segregazione del cromosoma 15: **presenza di disomia uniparentale materna per il cromosoma 15;**

	Genotipo				Interpretazione
Locus e posizione	Padre	Madre	Figlio	N.alleli paterni/materni	Commento
D15S818 (15q22.33)	2/3	1/3	3/3		non informativo
D15S643 (15q21.2)	1/2	3/3	3/3	-/due	isodisomia materna
D15S822 (15q13.1)	1/2	3/3	3/3	-/due	isodisomia materna
D15S657 (15q26.2)	1/2	3/4	3/4	-/due	eterodisomia materna
D15S817 (15q12)	2/4	1/3	1/3	-/due	eterodisomia materna
D15S816 (15q26.1)	2/2	1/2	1/2		non informativo
D15S659 (15q14)	2/4	1/3	1/3	-/due	eterodisomia materna
D15S1513 (15q13.1)	2/3	1/2	1/2		non informativo
D15S1365 (15q13.1)	1/3	2/4	2/4	-/due	eterodisomia materna

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Follow-up
La coppia decide di interrompere la gravidanza.

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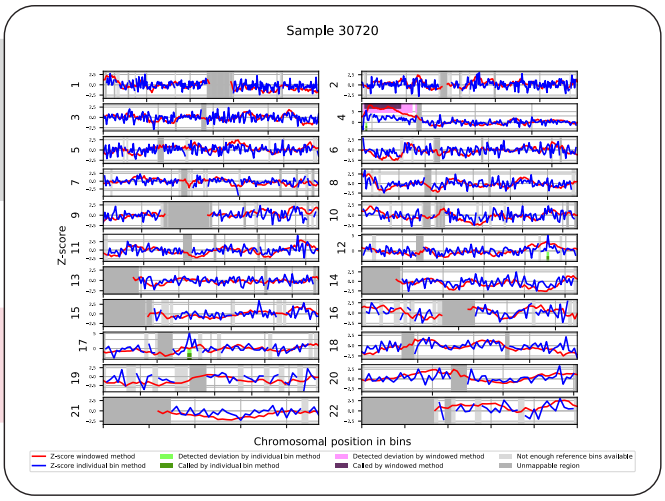
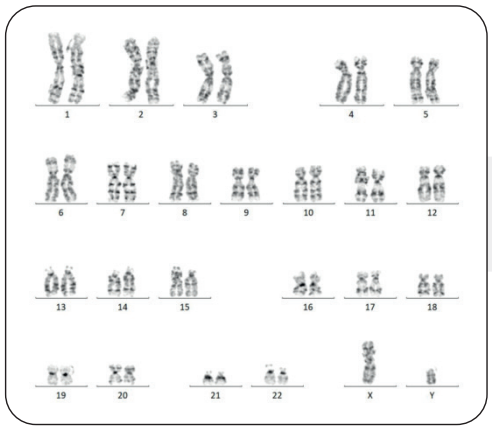
CASO CLINICO 5:
il Vera Prenatal Test Plus rileva una duplicazione sul braccio corto del cromosoma 4

La gestante si sottopone al Vera Prenatal Test Plus a 11 sett. di gravidanza.

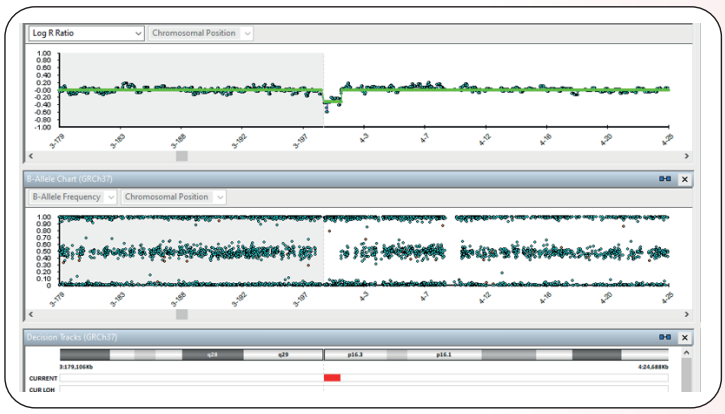
Vera Prenatal Test PLUS mostra una duplicazione di tutto il braccio corto del cromosoma 4.



La gestante si sottopone ad amniocentesi



I risultati del Cariotipo dal liquido amniotico non mostrano alcuna duplicazione



SNP-Array
arr [GRCh37] 4p16.3 (48,283-1,243,573)x1;

L'analisi ha evidenziato la presenza di una delezione, in eterozigosi, con un'estensione di circa 1.2 Mbp, presente a livello della citobanda p16.3 sul cromosoma 4.
Tale delezione coinvolge diversi geni, tra i quali ZNF141 [OMIM*194648], PDE6B [OMIM*180072], IDUA [OMIM*252800] e RNF212 [OMIM*612041].

La gestante, a seguito di consulenza genetica e dopo aver eseguito il cariotipo e lo SNP Array per la coppia (risultati WT), decide di interrompere la gravidanza.

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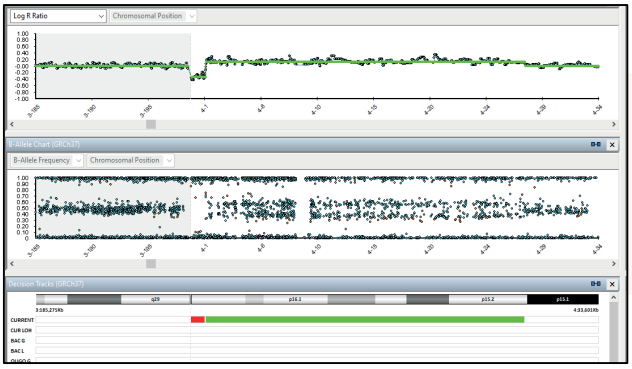
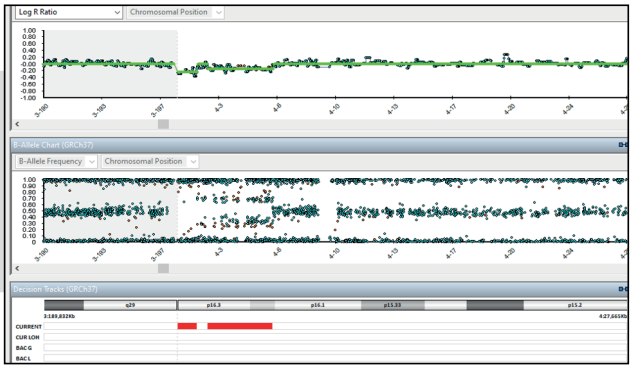
Visti i risultati contrastanti ottenuti dai due test e in accordo con la coppia si decide di eseguire analisi di SNP-Array su materiale abortivo e su materiale placentare recuperato durante proceduta IVG.

(a)



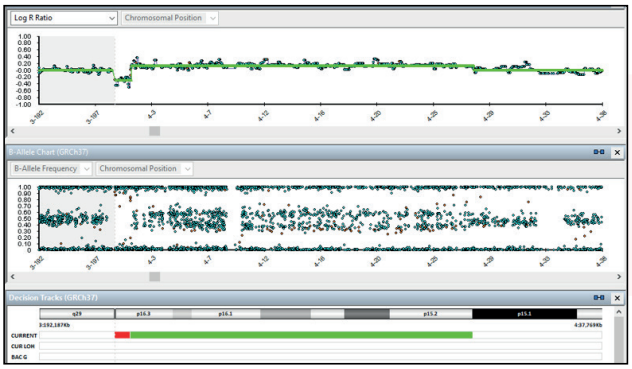
SNP-array:
DNA placenta campione 1

SNP-array:
DNA placenta campione 2



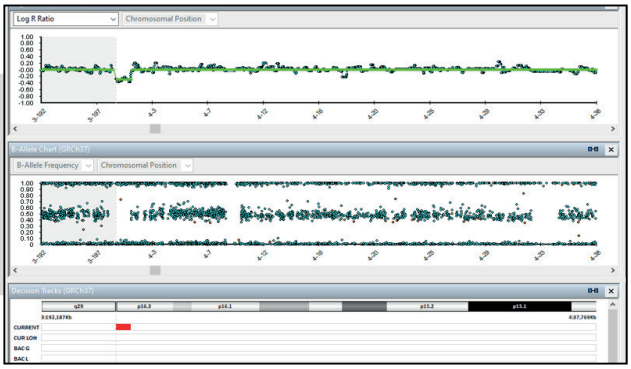
(b)

(c)



SNP-array:
DNA placenta campione 3

SNP-array:
DNA da aborto campione 1



(d)

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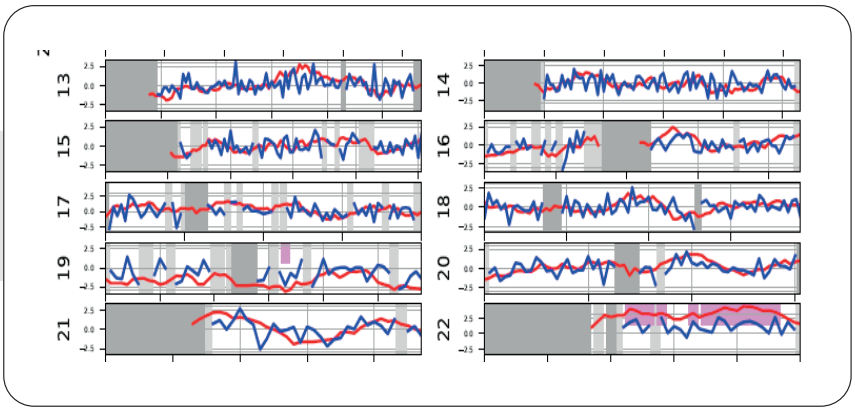
CASO CLINICO 6:
il Vera Prenatal Test Plus rileva una trisomia del cromosoma 22

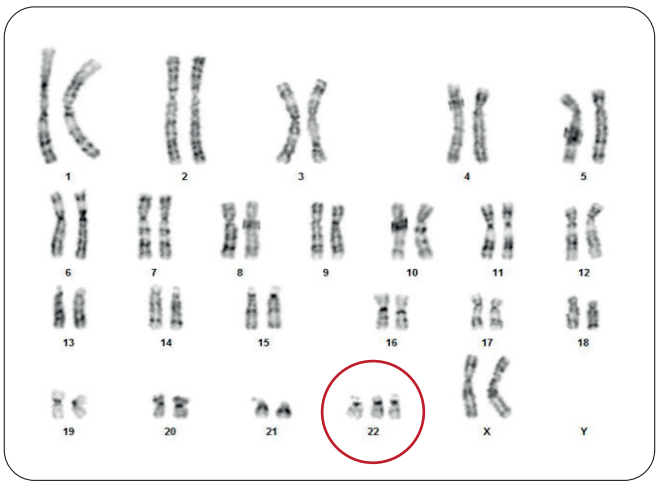
La gestante di 39 anni si presenta a 11 sett. di gravidanza.

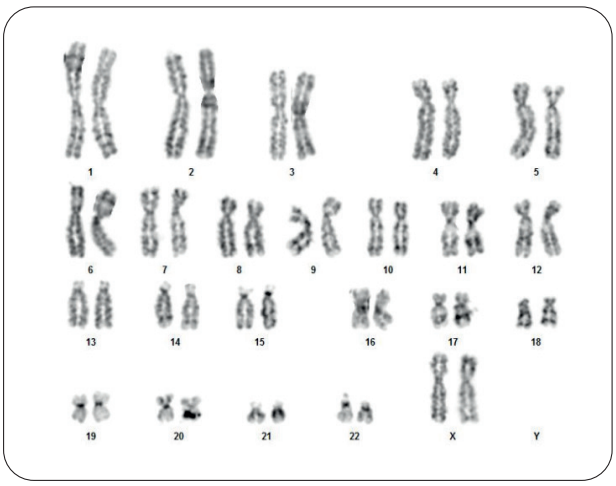
Vera Prenatal Test PLUS positivo per trisomia del cromosoma 22.



Aborto spontaneo a 15 settimane di gestazione.

La coppia decide di eseguire un cariotipo sul materiale abortivo che conferma una trisomia del cromosoma 22 a mosaico.
mos 47,XX, +22[3]/46,XX[17]





Follow-up
La gestante si sottopone a consulenza genetica per verificare il rischio di ricorrenza.

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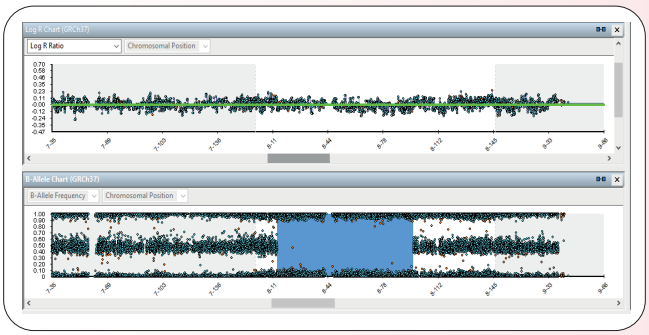
CASO CLINICO 7:
il Vera Prenatal Test Plus rileva una trisomia del cromosoma 8

La gestante di 33 anni si presenta a 12 sett. di gravidanza.

Vera Prenatal Test PLUS positivo per trisomia del cromosoma 8.

La gestante si sottopone ad amniocentesi.

SNP-Array al trio.



La diagnosi molecolare eseguita su DNA estratto da amniociti in coltura prelevati alla paziente in esame ha evidenziato la presenza del seguente sbilanciamento del numero di copie di sequenze genomiche:

Risultato sinottico secondo la nomenclatura internazionale (ISCN) 2016:
arr[GRCh37]8p23.3-p22(176,818-13,490,323)x2 htz pat 13.3Mb
arr[GRCh37]8p22-q22.1(13,490,995-96,718,566)x2 hmz pat 83.2Mb
arr[GRCh37]8q22.1-q24.3(96,725,932-146,288,066)x2 htz pat 49,6Mb

Descrizione del risultato:
L'analisi di SNP-Array condotta sul trio ha mostrato disomia iniparentale (UPD) paterna per le regioni terminali del cromosoma 8 e isodisomia (iUPD) paterna per la restante parte del cromosoma 8.

Cariotipo da liquido amniotico

Risultato: mos47,XY,+8[5]/46,XY[45]
Commento: Dall'analisi di 50 metafasi analizzate, da tre distinte colture, si evidenzia la presenza di due linee cellulari, una con una copia aggiuntiva del cromosoma 8 (10%) e l'altra con cariotipo maschile normale (90%).
Si consiglia consulenza genetica.

La gestante, a seguito di consulenza genetica e dopo aver eseguito il cariotipo e lo SNP Array per la coppia (risultati WT), decide di interrompere la gravidanza

ORPHA:96061

Livello di Classificazione: Malattia

Sinonimo/i : Sindrome di Warkany	applicabile o Sconosciuto	*UMLS:* C1096527
	Età di esordio: Infanzia, Neonatal	*MeSH:* C537940
Prevalenza: Sconosciuto	*ICD-10:* Q92.1	*GARD:* 5359
Trasmissione: Non	*OMIM:* -	*MedDRA:* 10053916

La trisomia 8 in mosaico è una malattia cromosomica caratterizzata dalla presenza di tre copie del cromosoma 8 in alcune cellule dell'organismo. È caratterizzata da dismorfismi facciali, lieve ritardo mentale, difetti urinari, scheletrici e articolari e cardiopatia. L'incidenza annuale varia tra 1/25.000 e 1/50.000. I maschi sono colpiti più frequentemente rispetto alle femmine (rapporto tra i sessi 5:1). I dismorfismi facciali consistono in un allungamento del cranio (scafocefalia), fronte prominente, ipertelorismo, occhi infossati (50%), naso largo con narici anteverse (60%), micrognazia (con labbra inferiori anteverse), padiglioni auricolari grandi e displasici, con antelici prominenti e grandi lobi. Altri possibili segni clinici sono l'agenesia del corpo calloso, la palatoschisi o il palato alto e ogivale (8%), il collo largo e corto, l'alta statura, il tronco sottile e allungato e il restringimento delle spalle e del bacino. Sono frequenti (40% e 25% rispettivamente) le anomalie urinarie (idronefrosi, reflusso vescico-ureterale) e dei grandi vasi. Sono comuni la camptodattilia (70%), l'artrogriposi delle articolazioni (che peggiora con il tempo), la plicatura palmare (nei neonati) e plantare profonda (75%), l'ipoplasia o l'agenesia delle rotule, i difetti vertebrali (65%: anomalie della segmentazione, anomalie costali, scoliosi...), l'opacità corneale e lo strabismo. La maggior parte dei pazienti presenta un ritardo mentale moderato (QI tra 50 e 75), mentre alcuni hanno un'intelligenza normale

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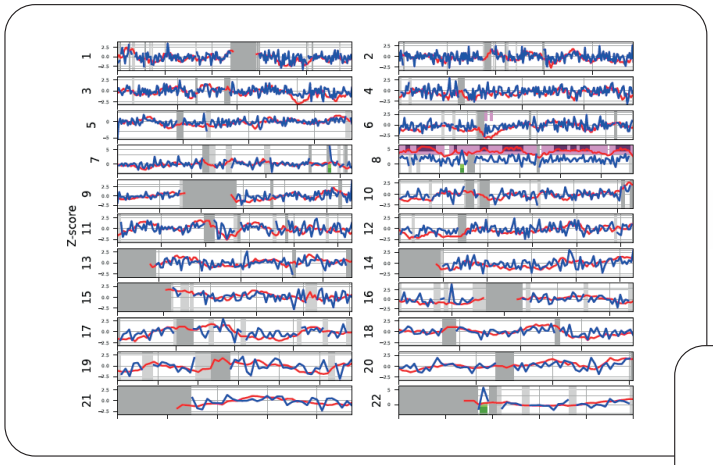
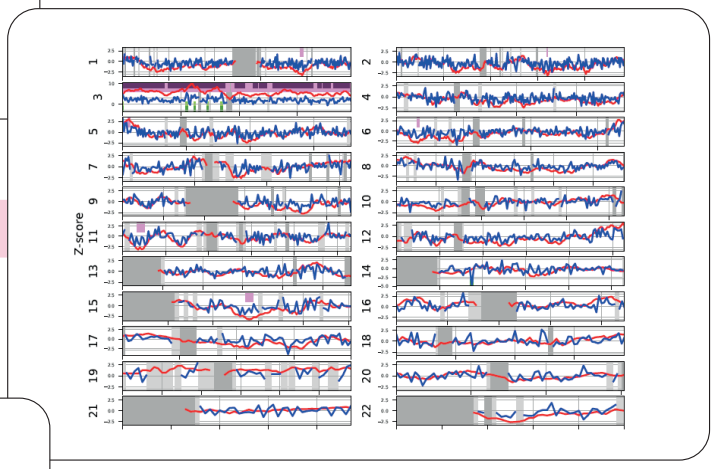
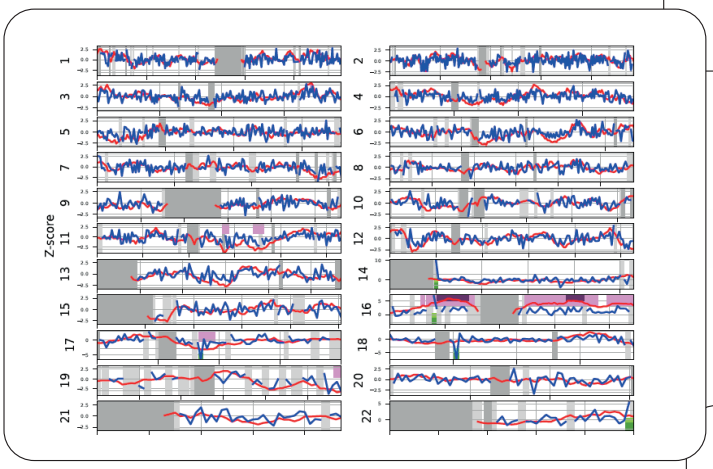
Ci sono altri casi dove però...



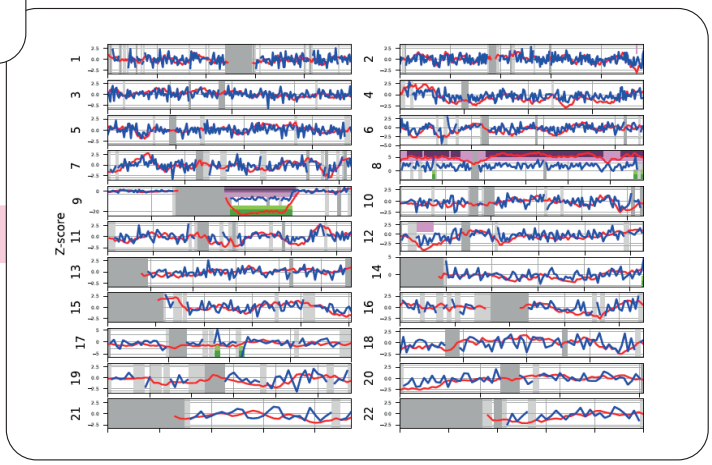
Trisomy chr8



Trisomy chr3



Trisomy chr16



Trisomy chr8, del chr 9 (35MB)

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Case Report

Non-Invasive Prenatal Screening: The First Report of Pentasomy X Detected by Plasma Cell-Free DNA and Karyotype Analysis

Luigia De Falco [1,*], Teresa Suero [1,2], Giovanni Savarese [1,2], Pasquale Savarese [1,2], Raffaella Ruggiero [1,2], Antonella Di Carlo [1,2], Mariasole Bruno [1,2], Nadia Petrillo [1,2], Monica Ianniello [1,2], Ciro Scarpato [3], Camilla Sarli [4,5] and Antonio Fico [1,2]

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5 CEINGE Biotecnologie Avanzate, 80131 Naples, Italy
* Correspondence: defalcol@centroamess.it

Abstract: Pentasomy X is a sex chromosome anomaly caused by the presence of three extra X chromosomes in females (49,XXXXX instead of 46,XX) and is probably due to a nondisjunction during the meiosis. So far, only five cases prenatally diagnosed were described. The main features in 49,XXXXX karyotype include severe intellectual disability with delayed speech development, short stature, facial dysmorphisms, osseous and articular abnormalities, congenital heart malformations, and skeletal and limb abnormalities. Prenatal diagnosis is often difficult due to the lack of a clear echographic sign like nuchal translucency (NT), and mostly cases were postnatally described. We report the first case of a 49,XXXXX female that was detected by non-invasive prenatal screening (NIPS), quantitative fluorescence polymerase chain reaction (QF-PCR) and a fetal karyotype.

Keywords: non-invasive prenatal screening (NIPS); sex chromosome anomaly; prenatal screening; quantitative fluorescent-polymerase chain reaction (QF-PCR); karyotype

check for updates

Citation: De Falco, L.; Suero, T.; Savarese, G.; Savarese, P.; Ruggiero, R.; Di Carlo, A.; Bruno, M.; Petrillo, N.; Ianniello, M.; Scarpato, C.; et al. Non-Invasive Prenatal Screening: The First Report of Pentasomy X Detected by Plasma Cell-Free DNA and Karyotype Analysis. *Diagnostics* **2022**, *12*, 1591. https://doi.org/10.3390/diagnostics12071591

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1. Introduction

Pentasomy X is a sex chromosome anomaly caused by the presence of three extra X chromosomes in females (49,XXXXX instead of 46,XX) and is probably due to a nondisjunction during the meiosis, either maternal or combined maternal and paternal in origin [1,2]. The true incidence of pentasomy X is unknown but an approximate incidence of 1 in 85,000 was reported comparing to 49,XXXXY syndrome in male live births [3].

The diagnosis is usually made postnatally when specific finding are observed: intellectual disability, variable growth deficiency, Down syndrome-like facial dysmorphy, hypogenitalism and other malformations, especially craniofacial anomalies, cardiovascular and skeletal anomalies [4]. According to a review of the postnatal pentasomy X cases published, intellectual disability and development retardation are the only clinical aspects in common in all the cases reported with a late symptoms onset [4]. Immunoglobulin anomalies, an increased susceptibility to infection and very recently epilepsy and cerebral leukodystrophy have also been reported [5]. Approximately less than 40 cases have so far been reported in the literature [6] with only five pentasomy X cases diagnosed prenatally, because of the absence of indicative echographic patterns for abnormalities caused by the chromosomal deviations which limits the possibility of the prenatal diagnosis [2,7–9].

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La Verde *et al. BMC Med Genomics* (2021) 14:93
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BMC Medical Genomics

RESEARCH ARTICLE Open Access

Performance of cell-free DNA sequencing-based non-invasive prenatal testing: experience on 36,456 singleton and multiple pregnancies

Marco La Verde[1], Luigia De Falco[2*], Annalaura Torella[3], Giovanni Savarese[2], Pasquale Savarese[2], Raffaella Ruggiero[2], Anna Conte[1], Vera Fico[1], Marco Torella[1] and Antonio Fico[2]

Abstract

Background: This paper describes the clinical practice and performance of cell-free DNA sequencing-based non-invasive prenatal testing (NIPT) as a screening method for fetal trisomy 21, 18, and 13 (T21, T18, and T13) and sex chromosome aneuploidies (SCA) in a general Italian pregnancy population.

Methods: The AMES-accredited laboratory offers NIPT in maternal blood as a screening test for fetal T21, T18, T13 and SCA. Samples were sequenced on a NextSeq 550 (Illumina) using the VeriSeq NIPT Solution v1 assay.

Results: A retrospective analysis was performed on 36,456 consecutive maternal blood samples, including 35,650 singleton pregnancies, 800 twin pregnancies, and 6 triplet pregnancies. Samples were tested between April 2017 and September 2019. The cohort included 46% elevated-risk and 54% low-risk patients. A result indicative of a classic trisomy was found in 356 (1%) of singleton or twin samples: 254 T21, 69 T18, and 33 T13. In addition, 145 results (0.4%) were indicative of a SCA. Of the combined 501 screen-positive cases, 484 had confirmatory diagnostic testing. NIPT results were confirmed in 99.2% (247/249) of T21 cases, 91.2% (62/68) of T18 cases, 84.4% (27/32) of T13 cases, and 86.7% (117/135) of SCA cases. In the 35,955 cases reported as unaffected by a classic trisomy or SCA, no false negative cases were reported. Assuming that false negative results would be reported, the sensitivity of NIPT was 100.00% for T21 (95% CI 98.47–100.0), T18 (95% CI 94.17–100.0), and T13 (95% CI 87.54–100.0). The specificities were 99.99% (95% CI 99.98–100.0), 99.98% (95% CI 99.96–100.0), 99.99% (95% CI 99.97–100.0), and 99.95% (95% CI 99.92–99.97) for T21, T18, T13, and SCA, respectively.

Conclusion: This retrospective analysis of a large cohort of consecutive patients who had whole-genome sequencing-based NIPT for classic trisomies and SCA shows excellent detection rates and low false positive rates.

Keywords: Whole-genome sequencing, Non-invasive prenatal testing, NIPT, Cell-free DNA, Screening, Aneuploidy, Trisomy, Down syndrome, Chromosome abnormality, VeriSeq NIPT solution

Background

During the last few decades, prenatal screening and diagnosis of fetal chromosome alterations and ultrasound detection of structural anomalies have rapidly evolved [1]. "Traditional" prenatal screening methods for chromosome anomalies combining maternal age, ultrasound

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Case Report

Detection of 46, XY Disorder of Sex Development (DSD) Based on Plasma Cell-Free DNA and Targeted Next-Generation Sequencing

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Abstract: Mutations in the *HSD17B3* gene cause *HSD17B3* deficiency and result in 46, XY Disorders of Sex Development (46, XY DSD). The diagnosis of 46, XY DSD is very challenging and not rarely is confirmed only at older ages, when an affected XY female presents with primary amenorrhea or develops progressive virilization. The patient described in this paper represents a case of discrepancies between non-invasive prenatal testing (NIPT) and ultrasound based fetal sex determination detected during prenatal screening. Exome sequencing was performed on the cell free fetal DNA (cffDNA), amniotic fluid, and the parents. Libraries were generated according to the manufacturer's protocols using TruSight One Kits (Illumina Inc., San Diego, CA, USA). Sequencing was carried out on NEXT Seq 500 (Illumina) to mean sequencing depth of at least 100×. A panel of sexual disease genes was used in order to search for a causative variant. The finding of a mutation (c.645 A>T, p.Glu215Asp) in *HSD17B3* gene in amniotic fluid as well as in cffDNA and both parents supported the hypothesis of the *HSD17B3* deficiency. In conclusion, we used clinical exome sequencing and non-invasive prenatal detection, providing a solution for NIPT of a single-gene disorder. Early genetic diagnoses are useful for patients and clinicians, contribute to clinical knowledge of DSD, and are invaluable for genetic counseling of couples contemplating future pregnancies.

Keywords: 17β-hydroxysteroid dehydrogenase deficiency; *HSD17B3* gene; non-invasive prenatal testing (NIPT); whole exome sequencing (WES); sex discordance

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1. Introduction

Deficiency of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) is a rare autosomal recessive 46, XY disorder of sex development (DSD) [1,2]. *HSD17B3* isoenzyme is present almost exclusively in the testes and converts Delta 4-androstenedione (D4) to testosterone [3,4]. To date several missenses, splice junction, and frame shift mutations in the *HSD17B3* gene have been reported thatcause *HSD17B3* deficiency [5]. Affected individuals have testes often found in the inguinal canal or in a bifid scrotum/labia majora [1–3] and normally developed Wolffian duct derivatives, but show undervirilization of the external genitalia, which often appear female with clitoromegaly, a blind-ending vagina, and at times, labial fusion [1–3]. They are usually raised as females [4], and virilization tends to occur at puberty due to peripheral conversion of androstenedione to testosterone by other 17ß-HSD isoenzymes [6]. Since its introduction into clinical practice in 2011, non-invasive

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CASE REPORT

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Detection of SRY-positive46,XX male syndrome by the analysis of cell-free fetal DNA via non-invasive prenatal testing

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Abstract
We report a new case of 46,XX male syndrome that was detected following an anomalous result by non-invasive prenatal testing (NIPT) and a discrepancy between the fetal karyotype and the ultrasonographic investigation. With the increasing use of NIPT, more gender discordances can be identified prenatally and be amenable to early therapy.

KEYWORDS
aneuploidies, circulating cell-free fetal DNA, non-invasive prenatal testing, sex discordance

1 | INTRODUCTION

Since the identification of circulating cell-free fetal DNA (cffDNA) in maternal blood, non-invasive prenatal testing (NIPT) by massive parallel sequencing (MPS) has permitted the early diagnosis of common fetal aneuploidies with high specificity and sensitivity.[1,2] In addition, NIPT using MPS can identify fetal sex aneuploidies (SCAs), although with a lower accuracy due to biological limits and little clinical experience.[3,4] Although maternal and fetal biological features could affect fetal sex aneuploidy detection,[5] disorders of sexual differentiation (DSD) may also produce a discordance between the NIPT sex genotype and ultrasonographic detection or fetal karyotype. DSD is found in approximately 1/2500 pregnancies.[6] 46,XX male syndrome, which was first described in 1964 by de la Chapelle, has a prevalence of 1:20 000 in newborn males,[7] with different clinical phenotypes, such as normal or ambiguous male external genitalia, infertility, or hypogonadism, presenting at birth or later during puberty.[8] Approximately 90% of cases show the presence of the sex-determining region Y (SRY) and are usually diagnosed after puberty when they develop hypogonadism, gynecomastia, and/or infertility.[9] SRY-negative subjects (10%) usually have ambiguous external genitalia to a variable degree, although a complete male phenotype can also be observed.[10]

In this paper, we described a novel case of 46,XX male syndrome arising from a sex discrepancy between NIPT results, with a partial Y chromosome detection, and the ultrasound examination of the fetus. Informed consent was obtained before performing these studies.

1.1 | Clinical report

A 40-year-old pregnant Caucasian woman at 11 + 2 weeks of gestation arrived to our center without particular indications except for maternal age. Considering the risk of invasive testing, the patient chose to undergo NIPT analysis. We performed whole genome sequencing (WGS) for the detection of aneuploidies of chromosomes 13, 18, 21, X, and Y using cffDNA from the maternal blood.[11] No aneuploidies were observed for chromosomes 21, 18, and 13 and

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CASO CLINICO 8:
il Vera Prenatal Test identifica un feto di sesso maschile con normale assetto cromosomico

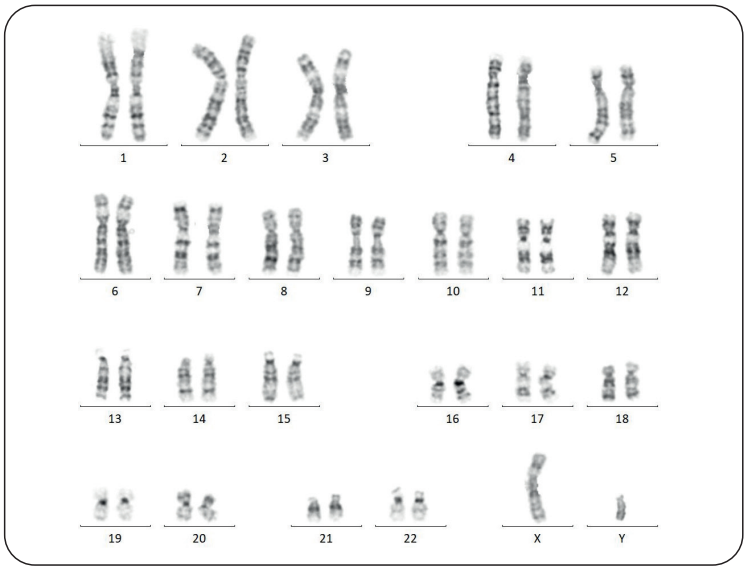
La gestante di 34 anni si presenta a 10 sett. di gravidanza.

Vera Prenatal Test: feto di sesso maschile, non vengono rilevate aneuploidie.

Ecografia morfologica mostra un feto di sesso **femminile**

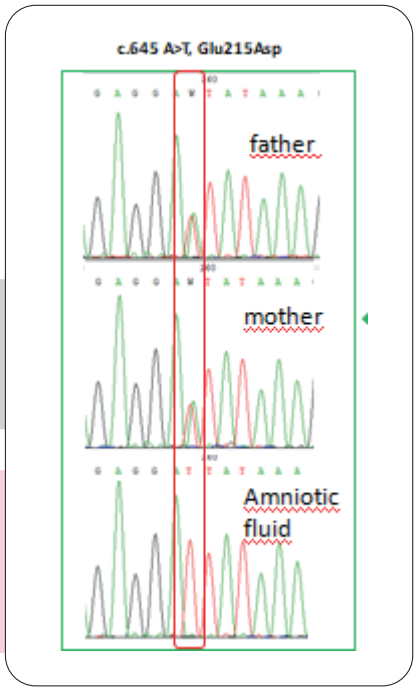
La gestante si sottopone ad amniocentesi e il cariotipo conferma i risultati del Vera Test.

SESSO MASCHILE 46, XY



Vera OMNIA Plus: rileva una mutazione nel gene HSD17B3 coinvolto nel differenziamento sessuale.

Il sequenziamento con metodo Sanger sul DNA estratto da amniociti, conferma che il feto presenta la mutazione in omozigosi, mutazione presente in eterozigosi nella coppia.



Follow-up
La coppia si sottopone a consulenza genetica e decidono di interrompere la gravidanza.
Avranno un rischio di ricorrenza del 25%.

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CASO CLINICO 9:
il Vera Prenatal Test non è riuscito a determinare l'assetto dei cromosomi 13, 18, 21 e dei cromosomi sessuali per la presenza di alterazioni a carico di diversi cromosomi autosomici.

La gestante di 28 anni si presenta a 16 sett. di gravidanza.

Vera Prenatal Test non è riuscito a determinare l'assetto dei cromosomi 13, 18, 21 e dei cromosomi sessuali.

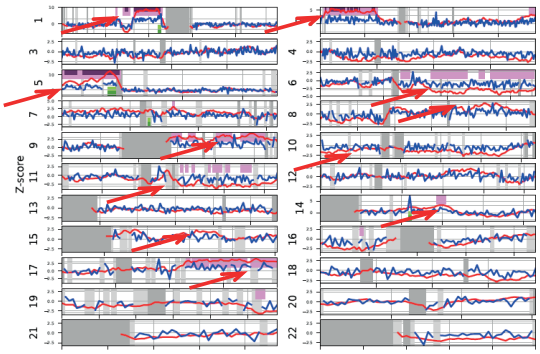
Vera Prenatal Test PLUS identifica diverse alterazioni a carico di numerosi cromosomi autosomici.

Referto Vera Prenatal Test®

CROMOSOMA	RISULTATO
Cromosoma 21	---
Cromosoma 18	---
Cromosoma 13	---
Cromosomi sessuali	---

CONCLUSIONI

Non è stato possibile determinare l'assetto dei cromosomi: 21, 18, 13 e dei cromosomi sessua per la presenza di anomalie a carico di alcuni cromosomi autosomici, alterazioni verosimilmente di origine placentare. Pertanto, si consiglia consulenza genetica ed eventuale analisi del cariotipo fetale mediante tecnica invasiva (villocentesi / amniocentesi).



La gestante decide di sottoporsi a consulenza genetica e di eseguire un'amniocentesi.

Il feto risulta 46, XY.

La signora viene inviata a consulenza ematologica che conferma la presenza, nella gestante, di un linfoma non Hodgkin.

Il **Vera Prenatal Test** ha avuto un risultato anomalo per la presenza, nel sangue della gestante, di DNA tumorale.

Table 3. Incidence of leading types of maternal cancer during pregnancy (data from Pavlidis, 2002).

Type of Cancer	Incidence
Breast cancer	1:3000–10,000
Cervical cancer	1.2:10,000
Hodgkin's disease	1:1000–6000
Malignant melanoma	2.6:1000
Leukemia	1:75,000–100,000
Ovarian cancer	1:10,000–100,000
Colorectal cancer	1:13,000

The rate of diagnosing a pregnancy-associated malignancy during NIPT is between 1 for every 1000 or 2000 20- to 40-year-old women. furthermore, a diagnosis of multiple aneuploidies carries a 20-44% risk of maternal cancer according to a study by Bianchi et al.

Matthew Cserhati, Calculation of Fetal Fraction for Non-Invasive Prenatal Testing, BioTech (Basel). 2021 Aug 9;10(3):17. doi: 10.3390/biotech10030017

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Casi clinici **Vera-OMNIA Prenatal Test**
Patologie monogeniche a trasmissione ereditaria o de novo

CASO CLINICO 10:
il Vera OMNIA identifica due mutazioni nel gene CFTR, responsabile della Fibrosi Cistica.

La gestante di 30 anni si presenta a 21 sett. di gravidanza, la morfologica rileva intestino iperecogeno.

Vera OMNIA identifica 2 mutazioni nel gene CFTR.

RISULTATI
L'analisi del DNA libero circolante (cfDNA) eseguita sul campione biologico in esame, ha RILEVATO le seguenti mutazioni:

-CFTR p Phe508del (c1521_1523delCTT,NM_000492.3, rs113993960) in ETEROZIGOSI di origine materna.
-CFTR p Leu1077Pro (c.3230T>C, NM_000492.3, rs139304906) in ETEROZIGOSI di origine paterna.
-GJB2 (c.-22-2A>C, NM_004004.5. rs201895089) in ETEROZIGOSI di origine materna.

Sesso Fetale: Femmina

Frazione fetale: 14%

Coverage medio: >600X

Rischio di risultati: Falsi Positivi <0.1%

CONCLUSIONI
Le mutazioni rilevate nel gene CFTR sono compatibili con un risultato di RISCHIO ALTO per il feto, in quanto la patologia correlata, la Fibrosi Cistica, è associata ad ereditarietà autosomica recessiva, pertanto sono necessarie due mutazioni in trans nello stesso gene per dare malattia, oche tali varianti siano presenti in omozigosi nel feto.

Sequenziamento del gene CFTR nei genitori per l'analisi di segregazione

ANALISI DNA MATERNO

RISULTATI

GENE ID	VARIANTE GENICA RICERCATA	RISULTATO
CFTR	c.1521_1523delCTT	**Variante Presente**

L'analisi molecolare eseguita sul DNA estratto dal sangue periferico del paziente in esame, utilizzando le metodiche di seguito descritte e per quello che le stesse possono rivelare a livello genico, **ha evidenziato la variante c.1521_1523delCTT in eterozigosi nel gene CFTR. Si consiglia consulenza genetica.**

ANALISI DNA PATERNO

RISULTATI
L'analisi molecolare del gene CFTR ha rilevato, in eterozigosi, la presenza della mutazione c.3230 T>C (p.L1077P); pertanto, **il paziente in esame risulta portatore di Fibrosi Cistica con il seguente genotipo: c.[3230 T>C];[=].**

Il polimorfismo Tn è risultato 7T in omozigosi (genotipo non associato a patologia).

Commento:
Poiché la Fibrosi Cistica è una malattia ereditaria a trasmissione autosomica recessiva si consiglia di estendere l'analisi genetica ai consanguinei per l'identificazione dei portatori, nonchè al partner ai fini di un' eventuale procreazione.
Presso il nostro laboratorio è possibile eseguire, ove richiesto, un approfondimento dell'analisi molecolare del gene CFTR, mediante utilizzo di metodiche che abbiano un maggiore *detection rate* (sequenziamento diretto e ricerca di macrodelezioni del gene CFTR, *detection rate*:94%).

Si consiglia consulenza genetica

Il risultato del **VERA OMNIA** è confermato mediante amniocentesi.

La gestante si sottopone a consulenza genetica.
Le viene riferito che il feto sarà affetto da fibrosi cistica, decide di portare avanti la gravidanza.

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LE NOSTRE **RACCOMANDAZIONI...**

Primo Trimestre: Counseling

- NT/DUO-TEST
- VILLOCENTESI/AMNIOCENTESI
- NIPT e NT

Secondo Trimestre: Morfologica

- **Discordanza Sesso** → Contattare il laboratorio e ripetere il test; Eventuale amniocentesi
- **Alterazioni Ecografiche** → Counseling ed eventuale amniocentesi

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