Medico-legal implications of prenatal screening

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Conflict of Interest
Vasco Sá, 2009

Disclosure: No conflict of interest

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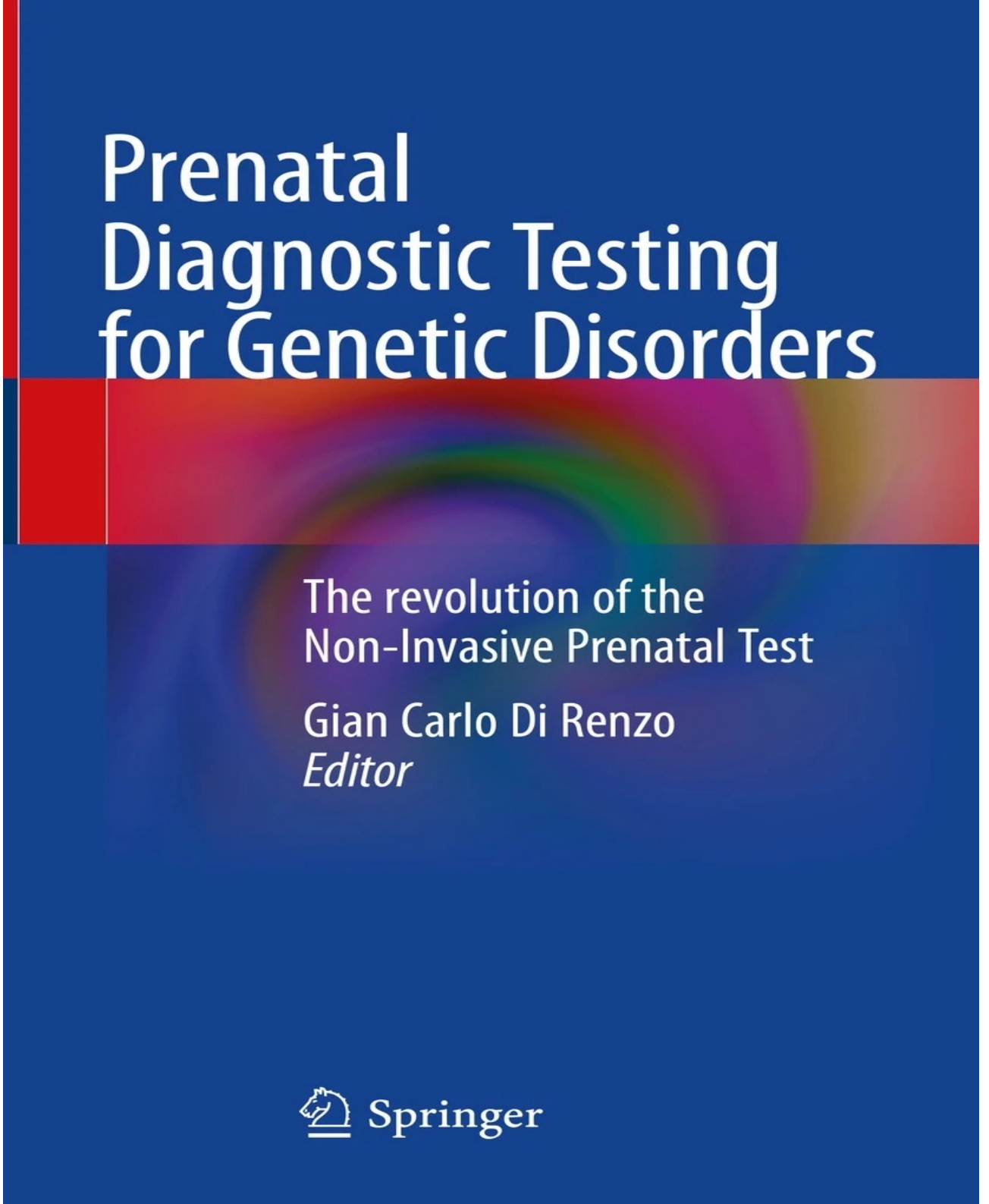

Prenatal
Diagnostic Testing
for Genetic Disorders
The revolution of the
Non-Invasive Prenatal Test
Gian Carlo Di Renzo
Editor
Springer

PREMISES

In the past century, numerous discoveries in the fields of genetics and technology and their applications to prenatal medicine have brought about a considerable revolution in prenatal diagnosis. The detection and prevention of prenatal disease has unveiled the mystery surrounding the fetus and the dimension of inviolability that characterized it in the past.

Discoveries with respect to the uterine world have contributed to an increase in scientific awareness of the fact that many problems of the child and of the adult have developed before birth.

The introduction of methods of indirect (biochemical) and direct (biophysical) evaluation of the fetus have allowed adequate investigation, undertaken with the use of an every-growing number of techniques based on fetal material sampling (amniocentesis, chorionic villus sampling, cordocentesis). It has been possible to benefit not only from sophisticated diagnostics but also from intra uterine medical and/or surgical treatment, in some conditions.

PREMISES

It was only in the mid-1960s that amniocentesis began to be used to detect fetal disease by spectrophotometric analysis of bilirubin on amniotic fluid, evaluating in this way fetal severity of RhD isoimmunization. In the same period, for the first time, chromosomal gender was determined on amniocytes through detection of Barr chromatin. However, in the 1970s the use of amniocentesis was very limited because it carried not only a high risk of abortion and prohibitive costs, but also because only women in their late-reproductive years were considered at high risk. Only at the end of the 1980s was a new approach (besides amniocentesis) of screening without any risk, that considered not only maternal age but also concentration of some factors of fetal–placental origin present in maternal peripheral blood, brought into use. In the 1990s, screening by a combination of maternal age and fetal nuchal translucency (NT) thickness at 11–14 weeks of gestation was introduced, and subsequently it has been shown that the combination of maternal age, fetal NT, and maternal serum biochemistry (free β-hCG and pregnancy associated plasma protein (PAPP-A)) in the first trimester has allowed the identification of about 85–90% of trisomy 21-affected fetuses

PREMISES

However, in the time period of the mid-1980s, the discovery of the presence of fetal cells in maternal blood during pregnancy and their isolation for genetic analysis produced a great revolution in prospective prenatal diagnosis. Various types of fetal cells have been identified in maternal blood, and various researchers have been occupied in the study of the identification, selection, and genetic analysis of fetal cells amenable for prenatal genetic testing.

Another possibility for non-invasive prenatal diagnosis began in 1997, when Dennis Lo and coworkers in Oxford showed the presence of cell-free fetal DNA (cfDNA) in maternal plasma and serum. From the studies following this discovery, it has been proved that fetal DNA is present in the maternal circulation from the first weeks of gestation and in major amounts with respect to that recovered from fetal cells. Moreover, free fetal DNA has the advantage that it degrades within a few hours of delivery, and therefore it cannot interfere with prenatal diagnosis of subsequent pregnancies.

Discovery of fetal derived cell-free DNA (cfDNA) in maternal blood

THE LANCET

The Lancet, Volume 350, Issue 9076, Pages 485 - 487, 16 August 1997
doi:10.1016/S0140-6736(97)02174-0

Presence of fetal DNA in maternal plasma and serum

MRCP, Dr Y M Dennis Lo [a], Noemi Corbetta [d], MD Paul F Chamberlain [b], MRCOG Vik Rai [b], PhD Ian L Sargent [b], FRCP Pr
Christopher WG Redman [b], FRCPath James S Wainscoat [c]

Tsitologiia. 1995;37(3):232-6.

[Extracellular DNA in the blood of pregnant women].

[Article in Russian]

Kazakov VI, Bozhkov VM, Linde VA, Repina MA, Mikhaĭlov VM.

Abstract

The level of extracellular DNA increases in the blood of women during pregnancy. By means of PCR, the full-size Alu repeats were observed among extracellular blood DNA repeats of pregnant women. Furthermore, with Tc65 type primer the PCR method allowed to observe in the blood DNA fragments flanked by inverted Alu repeats (inter Alu repeats). The presence of such a type of inter Alu repeats was estimated in the blood of women being in the first trimester of pregnancy only, but was not estimated among blood DNA fragments of women of the last trimester of pregnancy. It is discussed which types of cells may serve as a source of extracellular blood DNA (either trophoblast cells, lymphocytes, or decidual cells), the significance of such DNA for pregnancy being appreciated.

PMID: 8553462 [PubMed - indexed for MEDLINE]

PREMISES

Since then, non-invasive prenatal testing (**NIPT**) for fetal aneuploidy using cfDNA has been widely integrated into routine obstetrical care. Initially, cfDNA tests focused on chromosomal aberrations addressed by conventional prenatal screening methods, namely trisomy 21, trisomy 18, and trisomy 13. The scope soon expanded to include sex chromosome aneuploidy and microdeletion panels. Recently, genome-wide analysis has become available, expanding the scope of NIPT to address rare autosomal trisomies and large chromosomal imbalances. Because the technical ability to test for a condition does not necessarily correspond with a clinical benefit to a population or to individual pregnant women, the benefits and harms of screening programs must be carefully weighed before implementation. At the current time, scientific evidence regarding clinical performance of expanded cell-free DNA panels is lacking. Expanded cell-free DNA menus therefore create a dilemma for diagnosis, treatment, and counseling of patients which is a matter of big debate nowadays and calls for an ethical and effective expansion of the test.

Introduced for the first time in 2011, in a span of a decade the nowadays called NIPT (which refers practically only to the prenatal tests based on cfDNA) has expanded widely although irregularly in all the world rising many problems related to it applicability (particularly in low-middle income countries), costs, reliability (this pertaining mainly to the several in house tests flourished like mushrooms in many parts of the world), pre- and post-test counseling, ethical dilemmas, equity in access, and finally the "patentability" of the tests.
All these aspects required a clarification

Gian Carlo Di Renzo, preface to the Springer textbook, 2023

I am glad to see that in addition to science and clinical applications, this volume has also covered the ethics, societal, and cultural aspects of NIPT. With the rapid developments of science and technology, it is especially important to put such developments in the context of the human society and their ethical, legal, and societal impacts.

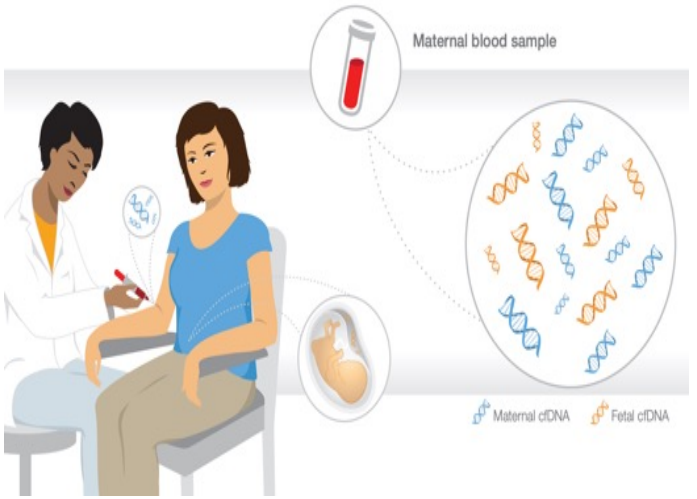
Dennis Lo, 2023

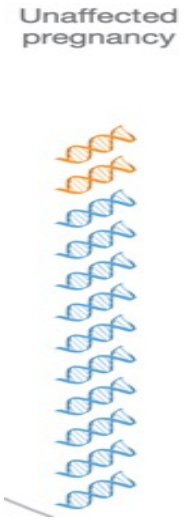
NIPT-Noninvasive Prenatal Testing

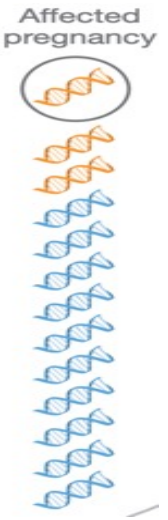
Benefits

Method; NIPT is a simple blood test
Risk: There is **zero risk** to the mother and baby
NIPT test helps determine an expecting mother's risk of having a baby with a common chromosomal conditions
Including:
Down syndrome (T21)
Edward syndrome (T18)
Patau Syndrome (T13).

Accuracy: Over 99% accurate







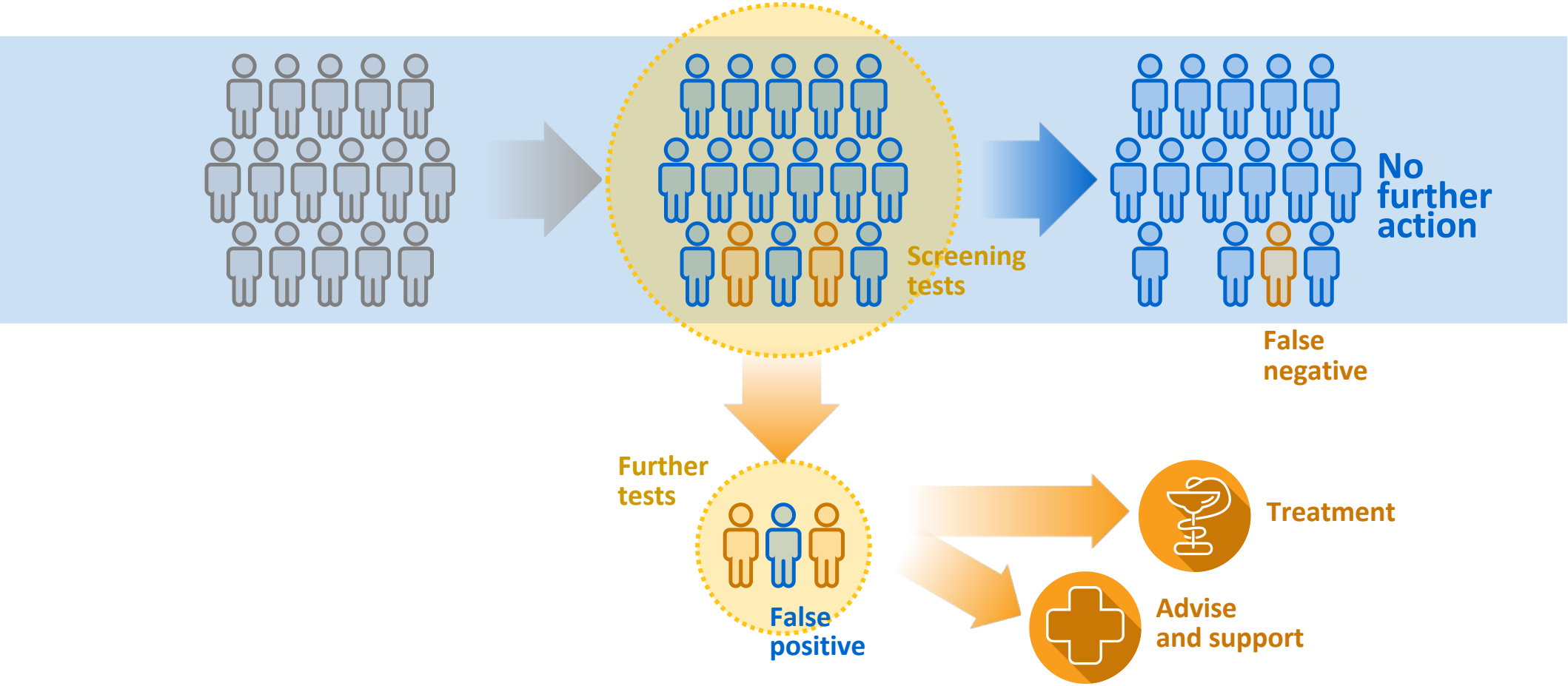
What is the topic about?

The introduction of a new molecular testing technique for early detection of fetal chromosome aneuploidy and sub-chromosomal conditions with high accuracy and no risk of miscarriage enabling early decision making

- Continuation of pregnancy
- Informed decision making
- Safer termination procedures
- Prepare for potential complications
- Schedule specialty services

Concept of a screening test

cfDNA based tests are screening tests



Evaluating screening programs

Potential benefits must be weighed against potential harms

- **The condition should be an important health problem[1]**
- **The natural history of the condition should be adequately understood[1]**
- **Facilities for diagnosis and treatment should be available[1]**
- **The screening program should respond to a recognized need[2]**
- **The objectives of screening should be defined at the outset[2]**
- **There should be scientific evidence regarding screening program effectiveness[2]**
- **The overall benefits of screening should outweigh the harm[2]**

1. Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Paper Number 34 WHO, 1968. 2. Andermann et al. Bull World Health Organ. 2008

Screening programs should address important health problems

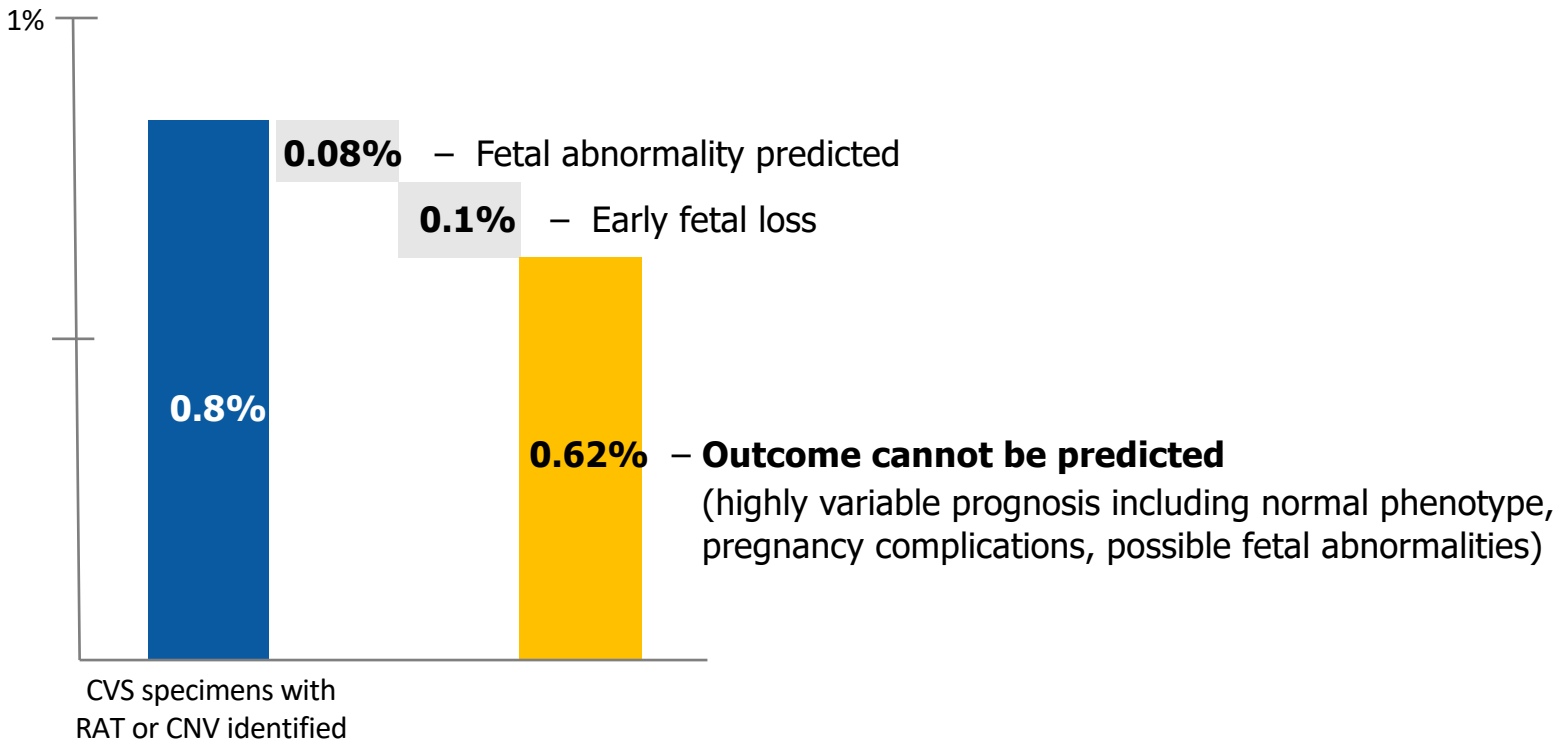
Most individual CNVs and RATs are exceedingly rare

Sex chromosome aneuploidies (SCAs)	**Prevalence**
– Monosomy X (45,X)	1/2,500[1] females
– Triple X Syndrome (47,XXX)	1/1,000[1] females
– Klinefelter Syndrome (47,XXY)	1/500 – 1/1,000[1] males
– Jacobs Syndrome (47,XYY)	1/1,000[1] males
Selected microdeletions and copy number variants (CNVs)	
– 22q11.2 deletion syndrome	1/1,000[2] - 1/2,500[3]
– 1p36 deletion syndrome	1/10,000[4]
– Prader Willi syndrome (15q11.2 – paternal)	1/10,000[5]
– Angelman syndrome (15q11.2 – maternal)	1/12,000[6]
– Cri-du-chat syndrome (5p15.3)	1/50,000[7]
– Jacobsen syndrome (11q23)	1/100,000[8]
– Langer Giedion syndrome (8q24.1)	unknown (rare)
Rare autosomal trisomies (RATs)	
– RAT for any chromosome confirmed in fetus	1/15,000[9]

Yaron et al, 2015; Di Renzo et al 2018

Natural history of screened conditions should be well understood

Outcomes often cannot be predicted if RAT or CNV is detected prenatally



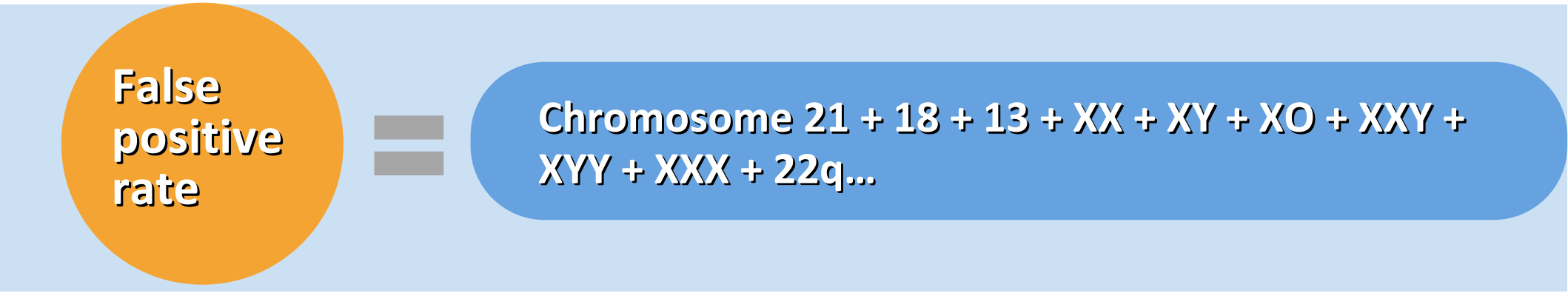
Benn P, Grati FR. Ultrasound Obstet Gynecol. 2018

Clinical issues

- Incidence rate of aneuploidies differs
- Lack of systematic and widespread prenatal screening programs
- Infrastructures creates boundaries
- Invasive prenatal testing not accepted for religious and socio-cultural reasons
- Genetic literacy very limited
- Equity in access
- Need to prevent birth of disabled children
- Suspension of clinical sequencing test in China: related consequences
- Fetal sex information in some areas

Clinical consequences of expanding cfDNA menus

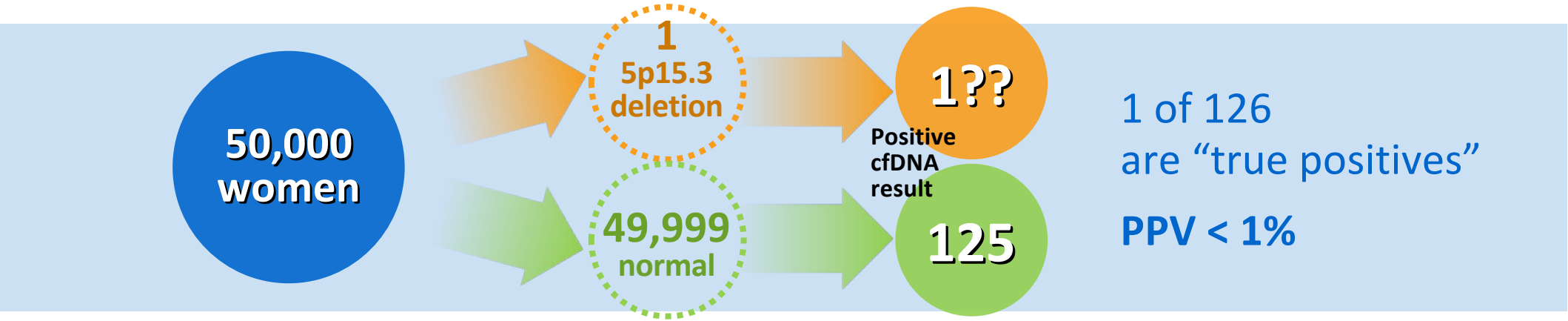
False positive rates are cumulative



Yaron et al, 2015; Di Renzo et al 2018

Clinical consequences of expanding cfDNA menus

PPV is extremely low for rare conditions



Example: 5p15.3 deletion

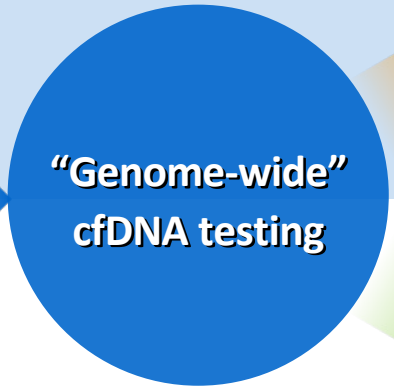
Prevalence: 1 in 50,000[1]

Perfomance: 0.24% false positive rate[2]

Yaron et al, 2015; Di Renzo et al 2018

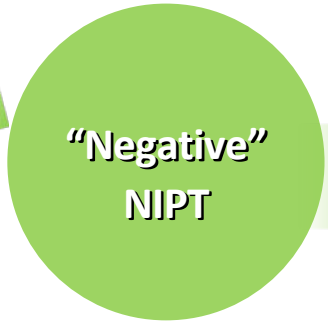
Examining clinical utility in a high risk population

"Genome-wide" analysis is not expected to alter management



Invasive test

- Confirmatory testing recommended
- Extremely low PPV for rare conditions



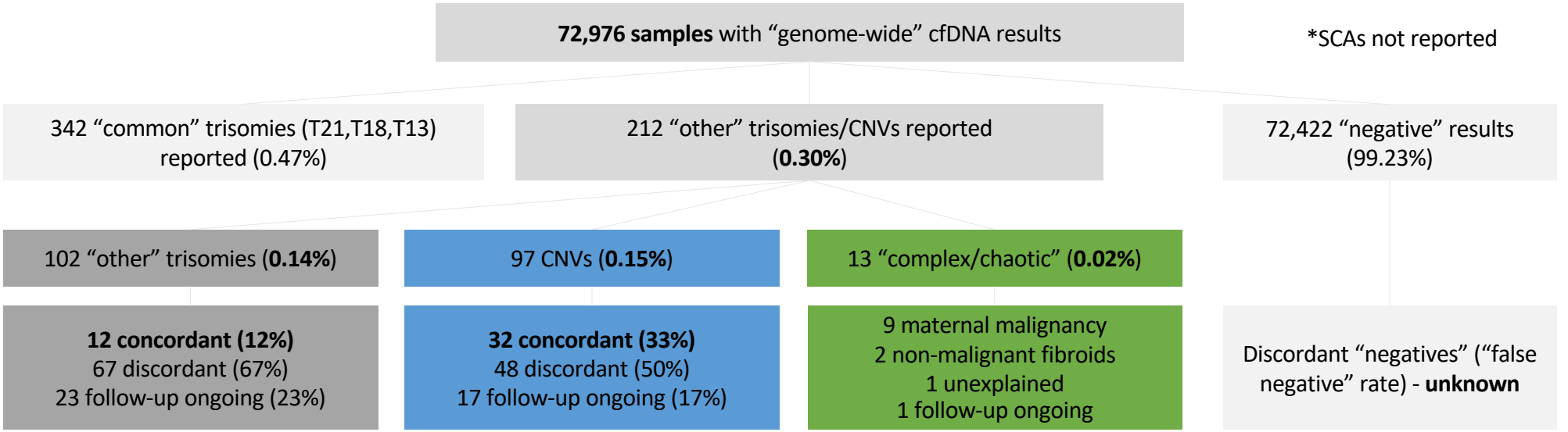
Invasive test

- Significant residual risk
- Detection rates low or unknown
- Unknown performance for mosaicism
- Small CNVs not addressed by NIPT

Potential for delayed diagnosis,
additional cost, and anxiety for patients

Examining clinical impact in a general population

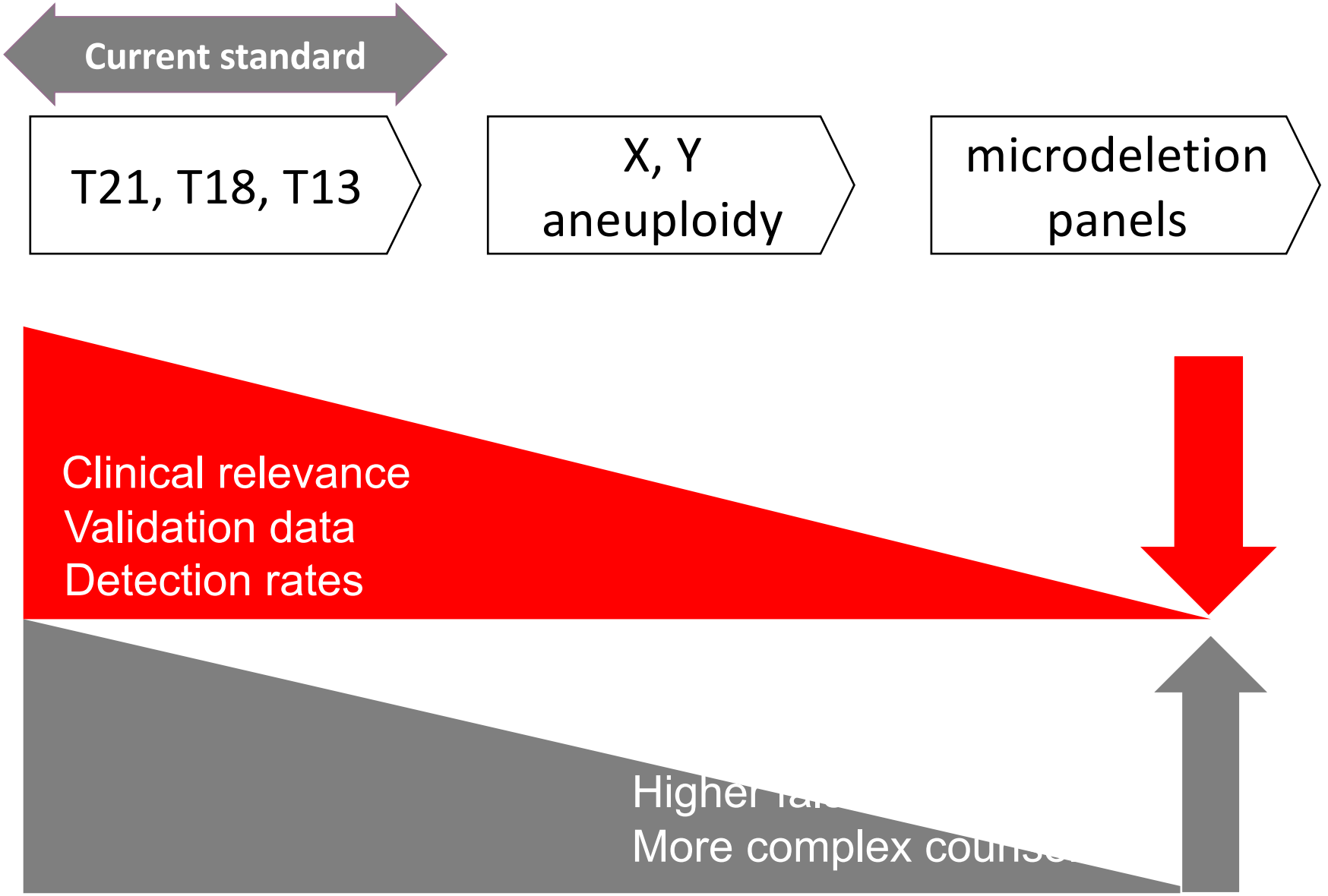
Dutch TRIDENT 2 study provides data for consideration



Points to consider:

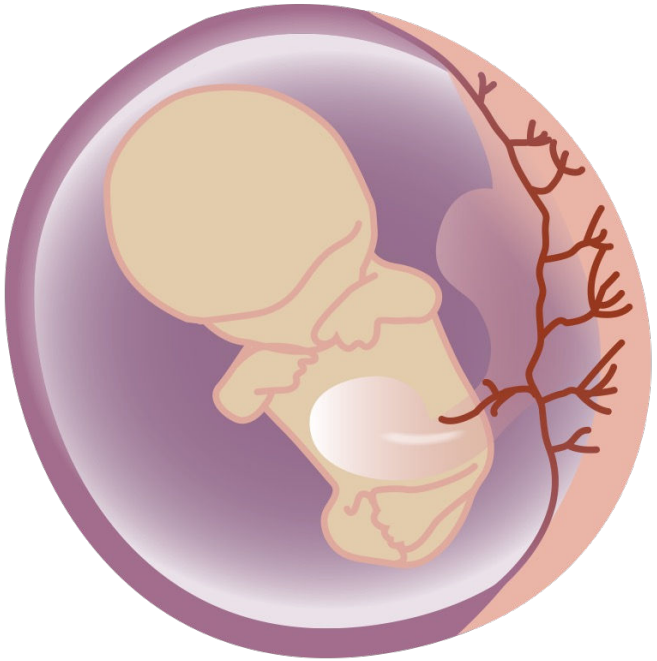
- **Low "screen positive" rate for RATs and CNVs in general population (0.30%)**
- **Increase in overall "false positive" rate (*at least* 0.16% for RATs and CNVs)**
- **Low positive predictive value (PPV) for RATs and CNVs**
- **Detection rate (sensitivity) is unknown (incomplete follow-up of "negative" results)**
- **Outcome of affected pregnancies unknown (did RAT or CNV impact phenotype or pregnancy management?)**
- **Patients should be counseled regarding possibility of findings unrelated to pregnancy (ie. malignancy)**

Expanding NIPT menus – issues and concerns



Di Renzo et al. AmJOG 2018, Jani, Di Renzo et al UOG 2020

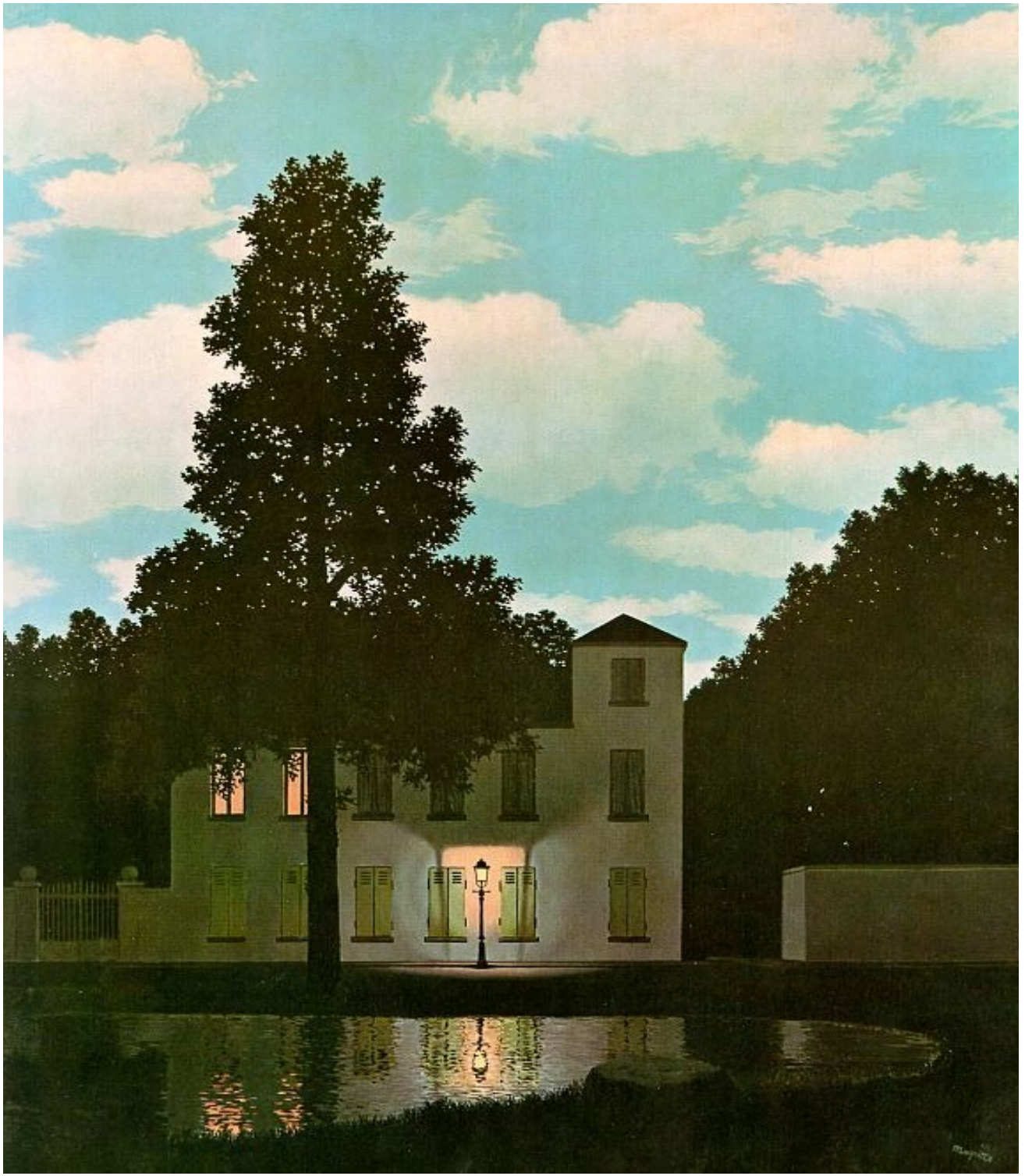
Placental Mosaicism



- cfDNA originates from placenta
  - Likely to be from trophoblast
  - Similar to “Direct prep” of chorionic villi
- Chromosomal makeup of placenta and fetus can be different
- Occurs more frequently with chromosomes 13 and 18, as compared to chromosome 21

Can lead to “false positive” and “false negative” NIPT results

1. Kalousek DK et al., Am J Hum Genet. 1989 Mar;44(3):338-43. 2. Wirtz et al, Prenat Diag. 1991 Aug;11(8):563-7.



Medico-legal implications of prenatal screening

ETHICAL, LEGAL and SOCIAL issues characterized the current prenatal screening

In the last years, new technologies such as non-invasive prenatal testing (NIPT) have become increasingly widespread and available

The possibility of **not having results** or to obtain **ambiguous results** to be confirmed by other methods should be adequately clarified before applying the test, possibly in a prenatal genetic counseling setting to enable informed choices.

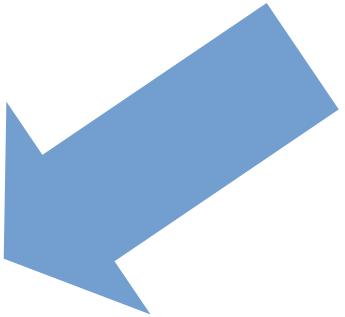
PRENATAL SCREENING IS NOT A DIAGNOSTIC TOOL

A negative result from screening does not mean a “certificate of health”

Medico-legal implications of prenatal screening

The ethical, legal and social implications (ELSI) in medicine include multiple aspects of informed decision-making.

The term ethical-legal-social implications can be associated with the term medico-legal complexities.



DUE TO …

INCOMPLETE OR MISINTERPRETED

COUNSELLING AND/OR TESTS RESULTS

(AMBIGUITY OF LABORATORY RESULTS,

ULTRASOUND FEATURES … **NOT ALL CAN BE DETECTED**!)

Medico-legal implications of prenatal screening

Genes (Basel). 2021 Feb; 12(2): 204.
Published online 2021 Jan 30. doi: 10.3390/genes12020204

PMCID: PMC7911180
PMID: 33573312

Ethical, Legal and Social Issues (ELSI) Associated with Non-Invasive Prenatal Testing: Reflections on the Evolution of Prenatal Diagnosis and Procreative Choices

Simona Zaami,[1] Alfredo Orrico,[2,3,*] Fabrizio Signore,[4] Anna Franca Cavaliere,[5] Marta Mazzi,[6] and Enrico Marinelli[1]

Prenatal screening: the advent of NIPT

NIPT has turned out to be a widespread screening tool for the most common fetal aneuploidy:

High sensitivity and specificity

Cost-effectiveness

Absence of risk of pregnancy loss associated with amniocentesis or chorionic villus sampling

However, NIPT cannot be considered as a

“prenatal diagnostic test”

First: COUNSEL ADEQUATELY

If **women/couple** are not offered clear information to help them make up their minds about prenatal screening techniques, about the risks and benefits of different approaches and the implications of all possible outcomes, they may not be able:

A) to think adequately

B) determine whether they really want the test results

C) how they would react to them

First: COUNSEL ADEQUATELY

Restricted access | Research article | First published online November 13, 2013

Imperfect informed consent for prenatal screening: Lessons from the Quad screen

ML Constantine, M Allyse, [...], and TH Rockwood (+2) View all authors and affiliations

Volume 9, Issue 1 | https://doi.org/10.1177/1477750913511339

Data from experiences with a “standard” blood draw such as serum screening seem to point to **poor levels of informed consent before the screening**, with many patients remarking that they did not really want to be tested or that, on the contrary, they refused to without being fully aware of its function

Informed consent to prenatal examinations has been shown to be associated with a **decreased level of decisional conflict**

First: COUNSEL ADEQUATELY

ULTRASOUND
in Obstetrics & Gynecology

isuog

Original Paper | Free Access

Knowledge of prenatal screening and psychological management of test decisions

K. Dahl, L. Hvidman, F. S. Jørgensen, U. S. Kesmodel

First published: 15 October 2010 | https://doi.org/10.1002/uog.8856 | Citations: 31

In conclusion, a high level of knowledge of prenatal screening was significantly associated with improved psychological management by means of lower decisional conflict and increased personal wellbeing. Knowledge was not associated with higher levels of worries in pregnancy. Further studies are needed on the importance of a high knowledge level for pregnant women making choices on participation in prenatal screening. Test–retest designs must be used to establish further evidence for how best to support all subgroups of pregnant women.

Second: DOCUMENTATION

Free Access

Informed consent: providing information about prenatal examinations

KATJA DAHL, ULRIK KESMODEL, LONE HVIDMAN, FREDE OLESEN

First published: 31 December 2010 | https://doi.org/10.1080/00016340600985198 | Citations: 30

POSSIBLE **CRITICAL POINTS** OF COUNSELLING AND INFORMED CONSENT:

MISSING INFORMATION

RESTRICTED INFORMATION

LIMITATIONS OF SCREENING TESTS NOT DISCUSSED

WRITTEN MATERIALS OFTEN INSUFFICIENT

Second: DOCUMENTATION

POSSIBLE **CRITICAL POINTS**
OF COUNSELLING AND INFORMED CONSENT:

MISSING INFORMATION
RESTRICTED INFORMATION
LIMITATIONS OF SCREENING TESTS NOT DISCUSSED
WRITTEN MATERIALS OFTEN INSUFFICIENT

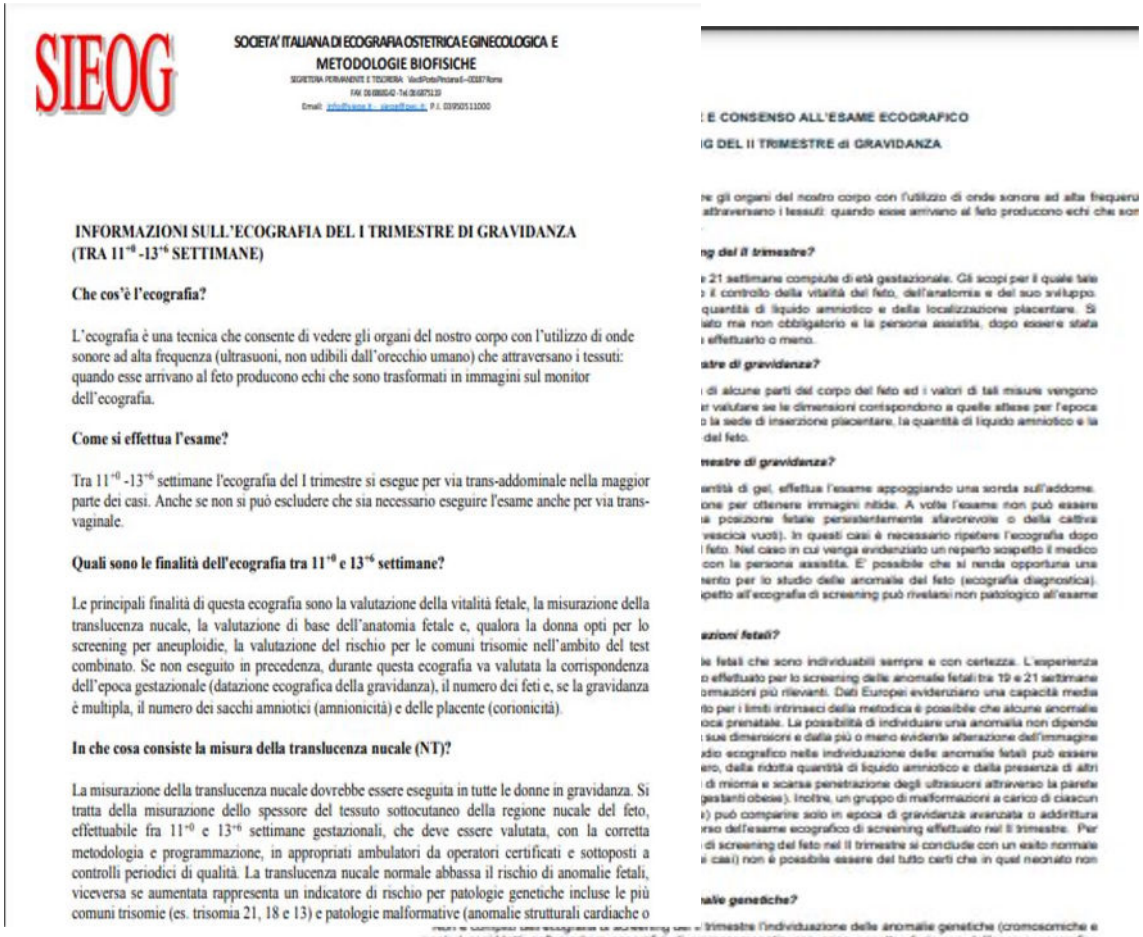
Good clinical practice may consist in **administer** and **restore** written materials on counselling

International and national authoritative society produced **inform consent schedules/models to refer**

Second: DOCUMENTATION

The Italian model – SIEOG

A written form on advantages and **INELIMINABLE LIMITS** of ultrasound screening in each trimester



SIEOG

SOCIETA' ITALIANA DI ECOGRAFIA OSTETRICA E GINECOLOGICA E METODOLOGIE BIOFISICHE

INFORMAZIONI SULL'ECOGRAFIA DEL I TRIMESTRE DI GRAVIDANZA (TRA 11^{+0} -13^{+6} SETTIMANE)

Che cos'è l'ecografia?

L'ecografia è una tecnica che consente di vedere gli organi del nostro corpo con l'utilizzo di onde sonore ad alta frequenza (ultrasuoni, non udibili dall'orecchio umano) che attraversano i tessuti: quando esse arrivano al feto producono echi che sono trasformati in immagini sul monitor dell'ecografia.

Come si effettua l'esame?

Tra 11^{+0} -13^{+6} settimane l'ecografia del I trimestre si esegue per via trans-addominale nella maggior parte dei casi. Anche se non si può escludere che sia necessario eseguire l'esame anche per via trans-vaginale.

Quali sono le finalità dell'ecografia tra 11^{+0} e 13^{+6} settimane?

Le principali finalità di questa ecografia sono la valutazione della vitalità fetale, la misurazione della translucenza nucale, la valutazione di base dell'anatomia fetale e, qualora la donna opti per lo screening per aneuploidie, la valutazione del rischio per le comuni trisomie nell'ambito del test combinato. Se non eseguito in precedenza, durante questa ecografia va valutata la corrispondenza dell'epoca gestazionale (datazione ecografica della gravidanza), il numero dei feti e, se la gravidanza è multipla, il numero dei sacchi amniotici (amnionicità) e delle placente (corionicità).

In che cosa consiste la misura della translucenza nucale (NT)?

La misurazione della translucenza nucale dovrebbe essere eseguita in tutte le donne in gravidanza. Si tratta della misurazione dello spessore del tessuto sottocutaneo della regione nucale del feto, effettuabile fra 11^{+0} e 13^{+6} settimane gestazionali, che deve essere valutata, con la corretta metodologia e programmazione, in appropriati ambulatori da operatori certificati e sottoposti a controlli periodici di qualità. La translucenza nucale normale abbassa il rischio di anomalie fetali, viceversa se aumentata rappresenta un indicatore di rischio per patologie genetiche incluse le più comuni trisomie (es. trisomia 21, 18 e 13) e patologie malformative (anomalie strutturali cardiache o

…E CONSENSO ALL'ESAME ECOGRAFICO

…G DEL II TRIMESTRE di GRAVIDANZA

…ne gli organi del nostro corpo con l'utilizzo di onde sonore ad alta frequenza …attraversano i tessuti: quando esse arrivano al feto producono echi che sono …

…ng del II trimestre?

…a 21 settimane compiute di età gestazionale. Gli scopi per il quale tale …il controllo della vitalità del feto, dell'anatomia e del suo sviluppo. …quantità di liquido amniotico e della localizzazione placentare. Si …lato ma non obbligatorio e la persona assistita, dopo essere stata …effettuarlo o meno.

…atre di gravidanza?

…di alcune parti del corpo del feto ed i valori di tali misure vengono …r valutare se le dimensioni corrispondono a quelle attese per l'epoca …o la sede di inserzione placentare, la quantità di liquido amniotico e la …del feto.

…mestre di gravidanza?

…antità di gel, effettua l'esame appoggiando una sonda sull'addome. …one per ottenere immagini nitide. A volte l'esame non può essere …la posizione fetale persistentemente sfavorevole o della cattiva …vescica vuota). In questi casi è necessario ripetere l'ecografia dopo …l feto. Nel caso in cui venga evidenziato un reperto sospetto il medico …con la persona assistita. E' possibile che si renda opportuna una …nento per lo studio delle anomalie del feto (ecografia diagnostica). …spetto all'ecografia di screening può rivelarsi non patologico all'esame

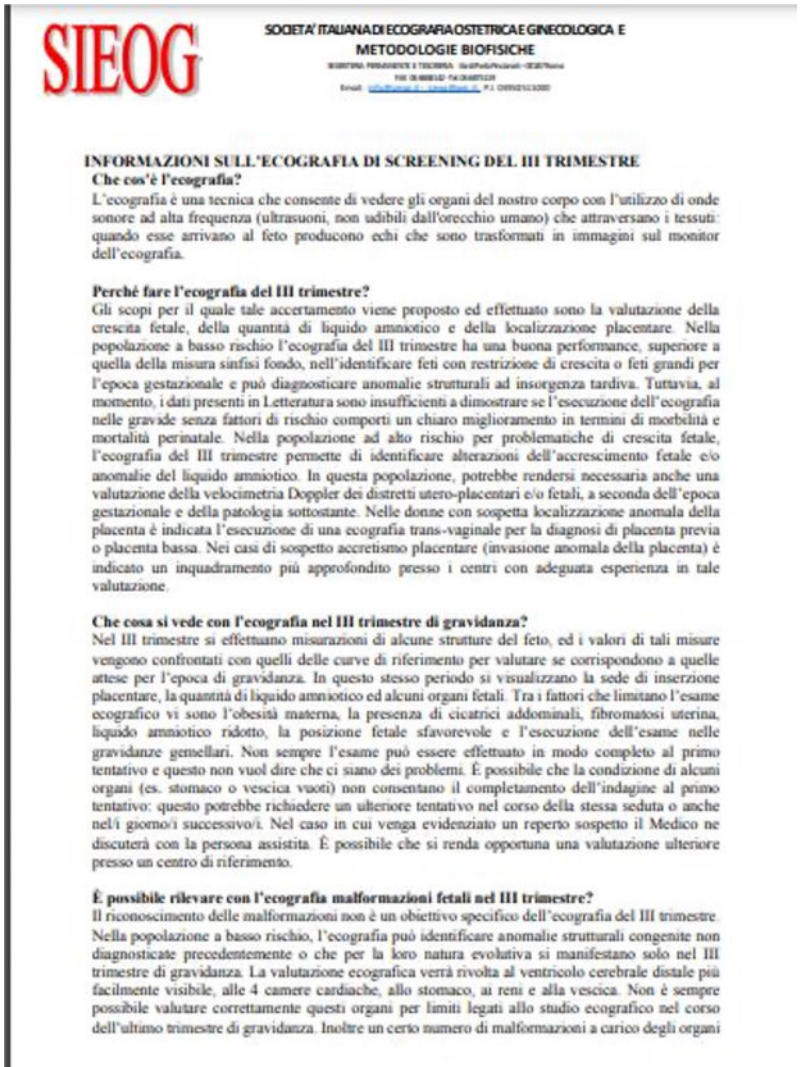
…azioni fetali?

…le fetali che sono individuabili sempre e con certezza. L'esperienza …o effettuato per lo screening delle anomalie fetali tra 19 e 21 settimane …ormazioni più rilevanti. Dati Europei evidenziano una capacità media …to per i limiti intrinseci della metodica è possibile che alcune anomalie …oca prenatale. La possibilità di individuare una anomalia non dipende …i sue dimensioni e dalla più o meno evidente alterazione dell'immagine …dio ecografico nella individuazione delle anomalie fetali può essere …ero, dalla ridotta quantità di liquido amniotico e dalla presenza di altri …di miioma e scarsa penetrazione degli ultrasuoni attraverso la parete …gestanti obese). Inoltre, un gruppo di malformazioni a carico di ciascun …) può comparire solo in epoca di gravidanza avanzata o addirittura …rso dell'esame ecografico di screening effettuato nel II trimestre. Per …di screening del feto nel II trimestre si conclude con un esito normale …i casi) non è possibile essere del tutto certi che in quel neonato non

…alie genetiche?

…trimestre l'individuazione delle anomalie genetiche (cromosomiche e non); i cosiddetti soft markers ecografici di cromosomopatia non sono oggetto di ricerca dell'esame ecografico effettuato per screening malformativo nel II trimestre. Inoltre non tutte le malattie genetiche presentano malformazioni rilevanti ed evidenziabili all'esame ecografico.

L'ecografia è innocua per il feto?



SIEOG

SOCIETA' ITALIANA DI ECOGRAFIA OSTETRICA E GINECOLOGICA E METODOLOGIE BIOFISICHE

INFORMAZIONI SULL'ECOGRAFIA DI SCREENING DEL III TRIMESTRE

Che cos'è l'ecografia?

L'ecografia è una tecnica che consente di vedere gli organi del nostro corpo con l'utilizzo di onde sonore ad alta frequenza (ultrasuoni, non udibili dall'orecchio umano) che attraversano i tessuti: quando esse arrivano al feto producono echi che sono trasformati in immagini sul monitor dell'ecografia.

Perché fare l'ecografia del III trimestre?

Gli scopi per il quale tale accertamento viene proposto ed effettuato sono la valutazione della crescita fetale, della quantità di liquido amniotico e della localizzazione placentare. Nella popolazione a basso rischio l'ecografia del III trimestre ha una buona performance, superiore a quella della misura sinfisi fondo, nell'identificare feti con restrizione di crescita o feti grandi per l'epoca gestazionale e può diagnosticare anomalie strutturali ad insorgenza tardiva. Tuttavia, al momento, i dati presenti in Letteratura sono insufficienti a dimostrare se l'esecuzione dell'ecografia nelle gravide senza fattori di rischio comporti un chiaro miglioramento in termini di morbilità e mortalità perinatale. Nella popolazione ad alto rischio per problematiche di crescita fetale, l'ecografia del III trimestre permette di identificare alterazioni dell'accrescimento fetale e/o anomalie del liquido amniotico. In questa popolazione, potrebbe rendersi necessaria anche una valutazione della velocimetria Doppler dei distretti utero-placentari e/o fetali, a seconda dell'epoca gestazionale e della patologia sottostante. Nelle donne con sospetta localizzazione anomala della placenta è indicata l'esecuzione di una ecografia trans-vaginale per la diagnosi di placenta previa o placenta bassa. Nei casi di sospetto accretismo placentare (invasione anomala della placenta) è indicato un inquadramento più approfondito presso i centri con adeguata esperienza in tale valutazione.

Che cosa si vede con l'ecografia nel III trimestre di gravidanza?

Nel III trimestre si effettuano misurazioni di alcune strutture del feto, ed i valori di tali misure vengono confrontati con quelli delle curve di riferimento per valutare se corrispondono a quelle attese per l'epoca di gravidanza. In questo stesso periodo si visualizzano la sede di inserzione placentare, la quantità di liquido amniotico ed alcuni organi fetali. Tra i fattori che limitano l'esame ecografico vi sono l'obesità materna, la presenza di cicatrici addominali, fibromatosi uterina, liquido amniotico ridotto, la posizione fetale sfavorevole e l'esecuzione dell'esame nelle gravidanze gemellari. Non sempre l'esame può essere effettuato in modo completo al primo tentativo e questo non vuol dire che ci siano dei problemi. È possibile che la condizione di alcuni organi (es. stomaco o vescica vuoti) non consentano il completamento dell'indagine al primo tentativo: questo potrebbe richiedere un ulteriore tentativo nel corso della stessa seduta o anche nel/i giorno/i successivo/i. Nel caso in cui venga evidenziato un reperto sospetto il Medico ne discuterà con la persona assistita. È possibile che si renda opportuna una valutazione ulteriore presso un centro di riferimento.

È possibile rilevare con l'ecografia malformazioni fetali nel III trimestre?

Il riconoscimento delle malformazioni non è un obiettivo specifico dell'ecografia del III trimestre. Nella popolazione a basso rischio, l'ecografia può identificare anomalie strutturali congenite non diagnosticate precedentemente o che per la loro natura evolutiva si manifestano solo nel III trimestre di gravidanza. La valutazione ecografica verrà rivolta al ventricolo cerebrale distale più facilmente visibile, alle 4 camere cardiache, allo stomaco, ai reni e alla vescica. Non è sempre possibile valutare correttamente questi organi per limiti legati allo studio ecografico nel corso dell'ultimo trimestre di gravidanza. Inoltre un certo numero di malformazioni a carico degli organi

Medico-legal implications derive from ...

Most medico-legal instances involving prenatal testing arise from **negligence** allegations

Healthcare operators are typically charged with failing to provide services that **meet the standards** of reasonable professional practice governing the healthcare provider's profession or specialty in force when the intervention was rendered

Physicians or genetic counselors may be accused of negligence in the provision of genetic counseling, e.g. **withholding information** from patients as to the potential reproductive risk based on carrier status or age, denying requests to carry out invasive procedures or neglect informing the patient about the need or availability of such procedures

Medico-legal implications derive from ...

Patterns may also develop involving **laboratory negligence** charges or genetic counseling based on misinterpreted laboratory results which lead the patients to make choices that they would not have made, had they had correct information, including the choice to bring the pregnancy to term.

These are usually referred to as *"**wrongful birth**" or "**wrongful life**"* instances.

“Wrongful abortion, wrongful birth, wrongful life”

Terms as “wrongful abortion, wrongful birth, wrongful life” arise from contexts in which the women/couple make choices that they would not have made, had they had correct information, including the choice to bring the pregnancy to term.

CMAJ. 2008 Nov 4; 179(10): 1027–1030.
doi: 10.1503/cmaj.080454

Wrongful birth litigation and prenatal screening

Mark Pioro, MA, Roxanne Mykitiuk, LLB LLM, and Jeff Nisker, MD PhD

BETTER OFF UNBORN?
AN ANALYSIS OF WRONGFUL BIRTH AND WRONGFUL LIFE CLAIMS UNDER THE AMERICANS WITH DISABILITIES ACT

DARPANA M. SHETH*

Missed diagnosis at antenatal screening – possible causes

Cases of failed prenatal detection of fetal anomalies at screening programmes were reported in literature, also recently with the most advanced technologies offered by novel tests, such as NIPT.

Biological causes, including fetoplacental mosaicism, insufficient or absent fetal fraction, and the presence of a vanishing twin, were described for discordant test results

Not all fetal morfologic anomalies can be detected during ultrasound screening

“The burden of psychological outcomes”...

Providing pregnant women with information may be associated with better psychological management.

Yet, **few studies** document the psychological outcomes of informed decisions in the area of prenatal screening, and some conflicting results have been reported on associations between knowledge and anxiety, as well as the importance of knowledge in improving the effectiveness of test decisions.

“The burden of psychological outcomes”...

BMJ. 2000 Feb 12; 320(7232): 407–412.

PMCID: PMC27284
PMID: 10669444

Psychological consequences for parents of false negative results on prenatal screening for Down's syndrome: retrospective interview study

Sue Hall, research associate,[a] Martin Bobrow, professor,[b] and Theresa M Marteau, professor[a]

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Hall S et al retrospectively analyzed the psychological consequences for parents of children with Down's syndrome of having received a **false negative result** on prenatal screening.

Parents of 179 children with Down's syndrome.

This study was the first systematic attempt to document the psychological consequences of false negative results in families experienced the birth of a baby with Trisomy 21

“The burden of psychological outcomes”...

a case of FALSE NEGATIVE RESULT

CASE REPORTS | MARCH 25 2023

Parental Psychological Distress of Missed Diagnosis of Down Syndrome at Antenatal Screening: A Rare, but Still Real Occurrence – A Case Report and Review of Literature

Subject Area: Genetics , Women's and Children's Health

Pasquale Giuseppe Macri; Valentina Tosto; Valentina Tsibizova; Arun Meyyazhagan; Gian Carlo Di Renzo

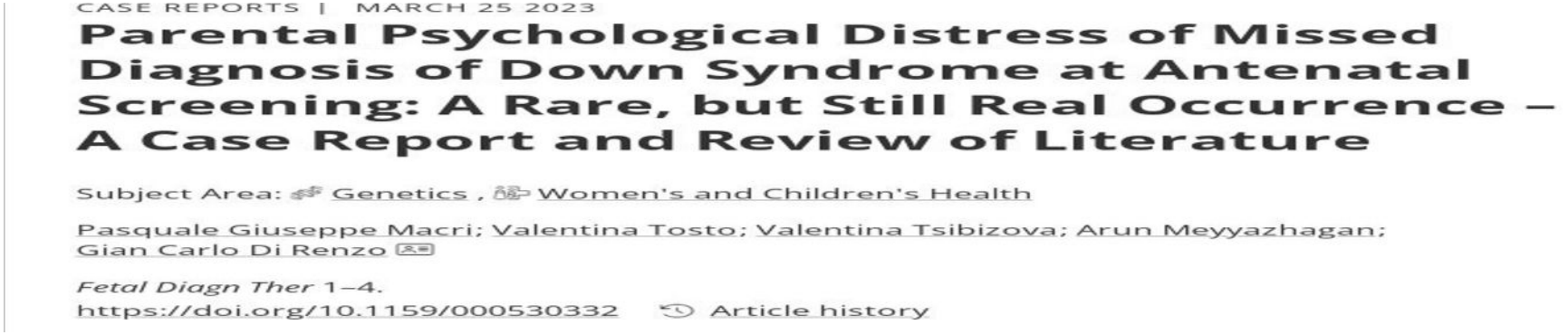
Fetal Diagn Ther 1–4.
https://doi.org/10.1159/000530332 Article history

A case of a **missed detection** of Down Syndrome at antenatal screening tests

Presentation of its heavy **medical** and **psychological longlife impact in all family nucleus**

“The burden of psychological outcomes”...

a case of FALSE NEGATIVE RESULT



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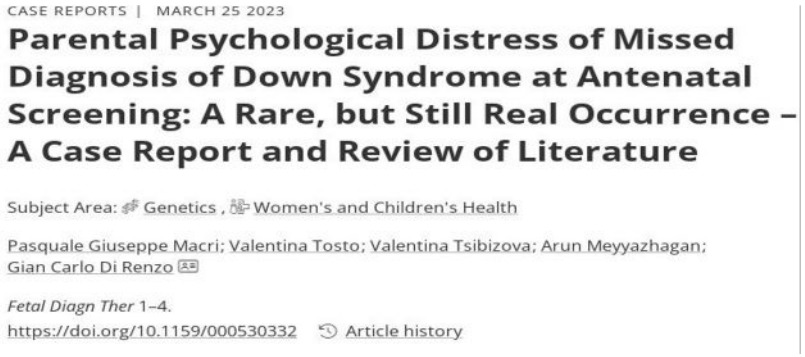
The parents filed a medico-legal action for the antenatal missed recognition of the Down Syndrome and the consequent biological and psychological damage suffered by both and the other young daughter.

As often happens in various medical contexts, legal actions are brought with the **hypothesis of malpractice and/or medical negligence**

“The burden of psychological outcomes”...

a case of FALSE NEGATIVE RESULT



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A description of the reaction and adaptation to the birth of a daughter with Trisomy 21.

From psychiatric consultations …

The mother: “As argued and deduced in the previous opinion, it is to be considered proven that Mrs ... was infringed in her right to be, during her second pregnancy, *promptly* and *correctly informed* about the state of health of the fetus, in order to *be able to freely* and *correctly self-determine* in relation to the continuation of the same pregnancy, in this case accepting the birth of a disabled daughter with the correlated dramatic change in her modus vivendi, work and existential performances or alternatively choosing to terminate the pregnancy within the terms provided for by law”.

“The burden of psychological outcomes”...

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The mother: “Mrs ... becomes aware only after the birth of her daughter, ***despite having undergone prenatal tests, numerous ultrasound examinations*, moreover performed by various professionals**. They could not prepare them during the pregnancy and if they had known, they would have decided to terminate. The more an event is sudden, unpredictable, with persistent effects as in the case in question, the greater the perception of poor self-efficacy of the subjects and the greater the risks for their health and for their physical and psychological well-being. The diagnosis caused a strong trauma in Mrs ..., linked to **the *discrepancy between the "ideal" child that she built as an object of love during pregnancy and the "imperfect" child that reality presented to her,*** with a consequent serious bereavement to be elaborated.

“The burden of psychological outcomes”...

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The mother: “... The lady suffered a huge shock that led her to face a long period of mental suffering and depression that crossed with a difficult marital situation, also due to the psychiatric problems of her husband who underwent numerous hospitalizations for depression in that period. and abuse of alcohol and drugs.

... Following her husband's hospitalizations and the high conflict between the couple, the lady is hospitalized in a mother-child community, to protect her from family conflicts ...The specialist psychodiagnostic assessment was able to confirm the existence and persistence of a post-traumatic stress disorder, defined sub specie temporis, as "chronic" or long-lasting and therefore comparable, for evaluation purposes, to permanent psychic disorder”.

“The burden of psychological outcomes”..

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From psychiatric consultations …

The husband: “Currently, Mr... is undergoing psycho-pharmacological and psychotherapeutic treatment due to the persistence of psychopathological disorders (anxiety, depression, feelings of despair, insomnia, poor appetite or hyperphagia, asthenia, anhedonia, difficulty concentrating, indecision, discontrolled impulses, low self-esteem) arose following the very serious condition of his little daughter ... A complicated post-traumatic stress disorder, of medium to severe degree, to which an anxious reactive graft depressive disorder is recognized ...”

“The burden of psychological outcomes’

a case of FALSE NEGATIVE RESULT

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The other young daughter: “ The girl suffered a vicarious traumatization following the traumatic birth of her little sister and the consequent lack of availability of the parents towards her. She needs a therapeutic space where she can re-elaborate what happened to her and her family”.

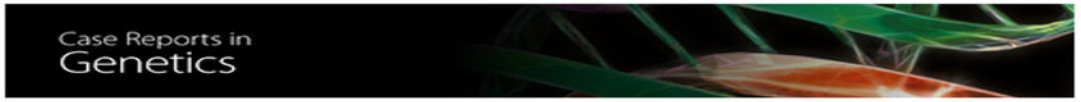
A FALSE NEGATIVE RESULT

Nowadays, false results at antenatal screening are really low, but healthcares should be aware to provide an accurate and comprehensive counseling about this possibility prior to undergoing these investigations.

Suzumori et al retrospectively investigated cases of false results in non-invasive prenatal testing for fetal trisomies 21, 13 and 18. Authors underlined the importance of genetic counseling with regard to false results for pregnant women/couples **prior to** undergoing NIPT

A FALSE NEGATIVE RESULT

Smith M et al described in 2014 the first case report of a patient whose fetus tested "negative" for Trisomy 21 by NIPT but was diagnosed postnatally with trisomy 21



Case Rep Genet. 2014; 2014: 823504.
Published online 2014 Feb 4. doi: 10.1155/2014/823504
PMCID: PMC3932282
PMID: 24649382

A Case of False Negative NIPT for Down Syndrome-Lessons Learned

Meagan Smith, Kimberly M. Lewis, Alexandrea Holmes, and Jeannie Visootsak*

As the medical community continues to embrace new technologies and incorporate them into daily clinical practice, it is imperative to ensure that the appropriate level of education is occurring for the provider ordering the test and the patient being offered the test. When knowledgeable medical professionals properly discuss the utility of NIPT and provide patients with anticipatory guidance regarding the possible outcomes, they enable the patient to make a more informed decision regarding the role of NIPT in their pregnancy.

Forecast

Effective and **ethical** expansion of NIPT

More genetic conditions included

Development of in house testing capabilities

Education of parents

More genetic counselors needed

Capacity building, investment and training

Key messages

The test based on cfDNA is superior and more accurate than any other prenatal screening methods and will quickly spread in HIC and LMIC for the forthcoming years

Although the extremely low false positive rate is an advantage, still remain a screening test not a diagnostic one

The widespread introduction of NIPT is changing the scenario and the consequences of prenatal screening and diagnosis

Genetic counseling should accompany the application of the test

Nations should implement regulations and oversight to ensure that NIPT fits into existing legal frameworks

All stakeholders should have a voice in crafting policies to ensure the ethical and equitable use of NIPT across the world

Di Renzo et al. AmJOG 2018, Jani, Di Renzo et al UOG 2020

Regarding the FALSE NEGATIVE RESULTS in screening tests

Assessment of the appropriateness of screening programs involves consideration of the harms as well as the benefits.

These harms include the risk of false-negative results, the consequences of which have remained underinvestigated.

Nowadays, the prenatal available screening texts show a good performance, with very low false negative (FN) results.

False negatives are evident even in high-quality screening programs. They may have the potential to delay the detection of abnormal conditions.

FN results also may lead to legal action being taken by those affected and may reduce public confidence in screening.

Their impact may be reduced by provision of full and well documented information about the benefits and limitations of screening programs and by increasing public education on these issues.

Learned lessons

A missed diagnosis at screening programmes sometimes generates:

severe long-life psychological, social and economic sequalae in all family member

complex medical-legal paths due to **PRESUMABLE** concept malpractice in "*wrongful birth*"

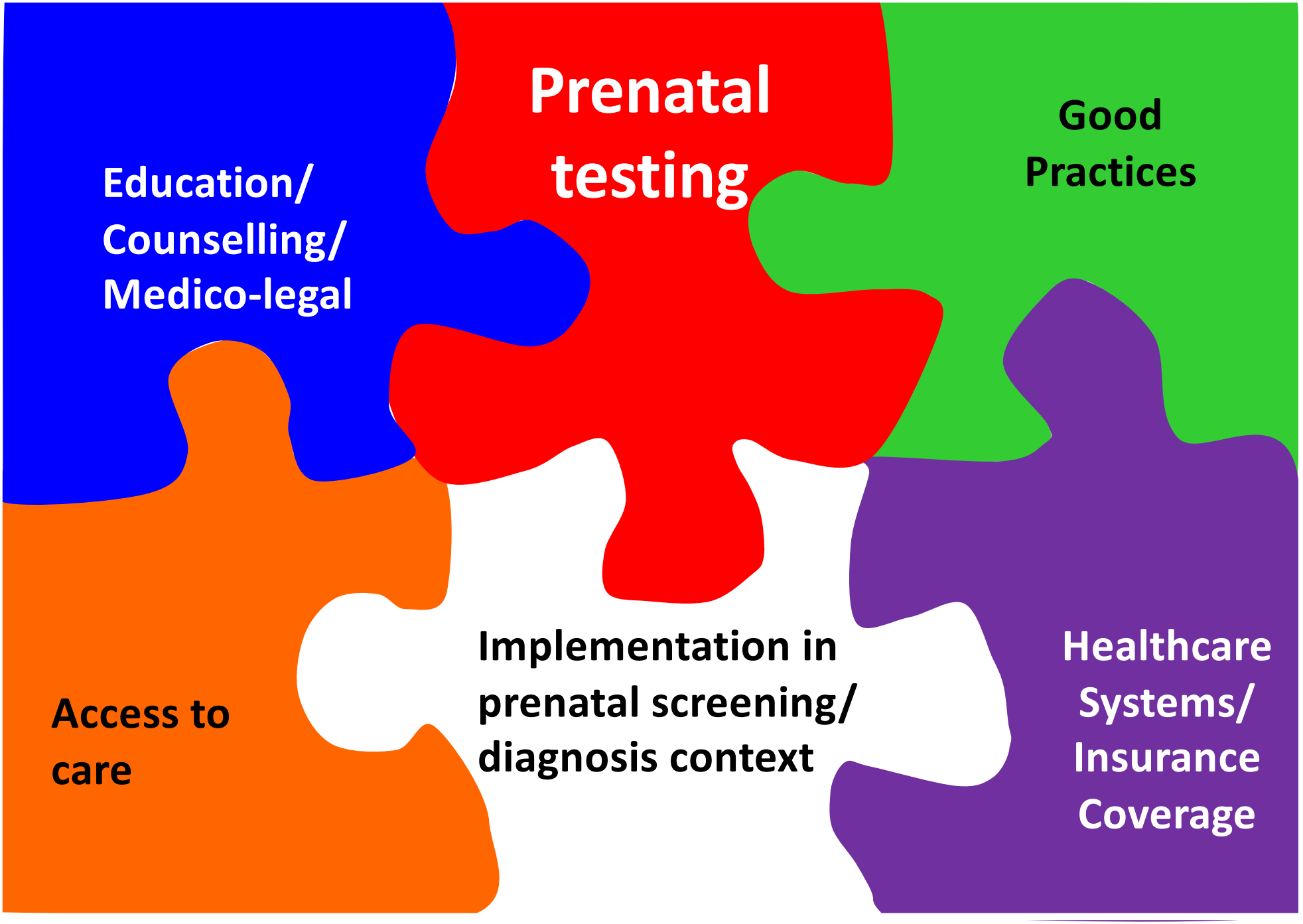
Considering the well-recognized role of screenings as a good reliable tool for early detection a huge number of fetal anomalies, but **WITHOUT DIAGNOSTIC CAPACITY**, medical malpractices **should not be advocated if patients were previously accurately informed**

Current and future essential objectives

Empowering interventions aimed to inform women/couple about prenatal screening, covering **ALL ASPECTS** - educational, medical, psychosocial, emotional

Healthcare professional **TRAINING**, **EDUCATION** and **PRACTICE** need to be improved and empowered

“It's a rare, BUT STILL A REAL OCCURENCE!”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Education/ Counselling/ Medico-legal
Good Practices
Access to care
Implementation in prenatal screening/ diagnosis context
Healthcare Systems/ Insurance Coverage

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