

# Sık görülen Anöploidilerin Noninvaziv Prenatal Taramasında cf-DNA Analizi



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# Prenatal Tanı?

Fetustaki,

- genetik veya nongenetik nedenlerin yol açtığı
- malformasyon ve hastalıkların
- gebeliğin mümkün olduğunca erken döneminde tanınmasıdır.

A. Malformasyonlar: Tanı → USG

**B. Kromozom anomalileri:**

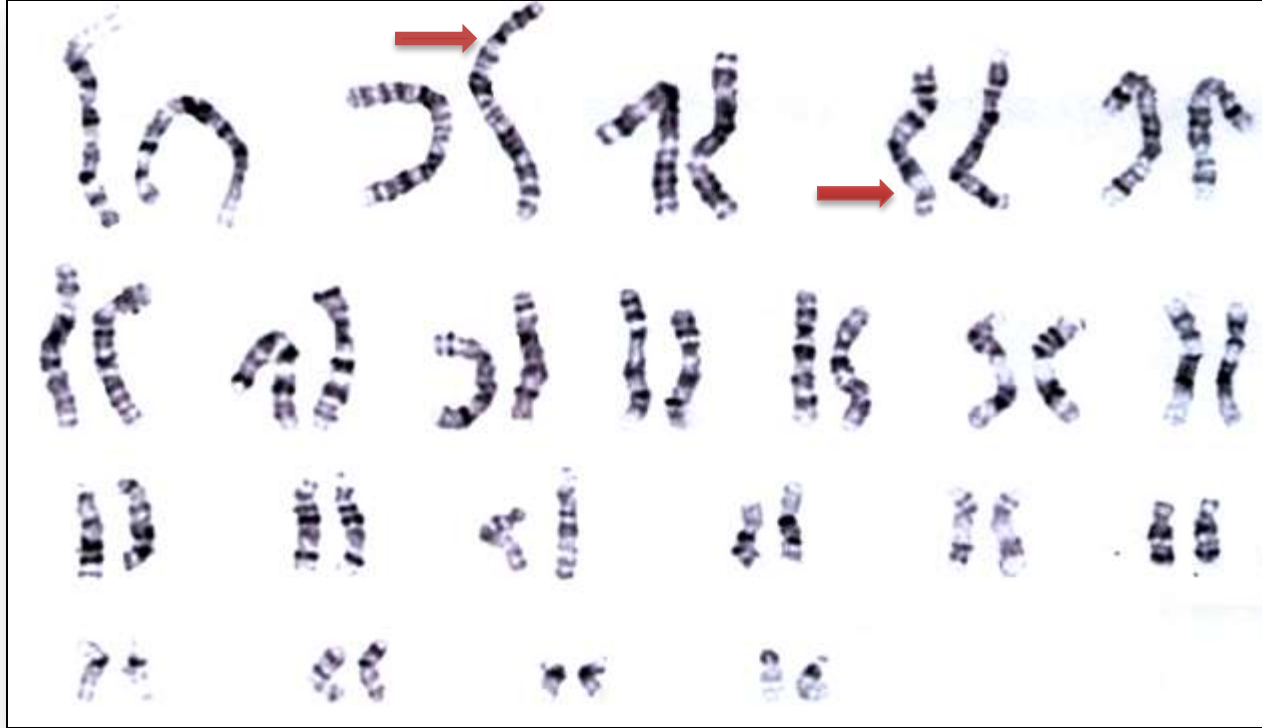
**Tanı → Fetal karyotipleme/aCGH/mikroarray**

C. Tek gen hastalıkları:

Tanı → DNA/enzim analizleri

**Prenatal tanı endikasyonu;** İleri anne yaşı+2'li testte artmış risk+ICSI  
(donuk embriodan)

**13. GH CVS Karyotip;** 46, --, t(2;4)(p23;q31.1)dn



**a-CGH endikasyonu;**  
Görünürde dengeli de  
novo resiprokal  
translokasyon

**a-CGH sonucu normal**

**22. GH, 2. düzey USG;** Ense plisi kalınlığında artış

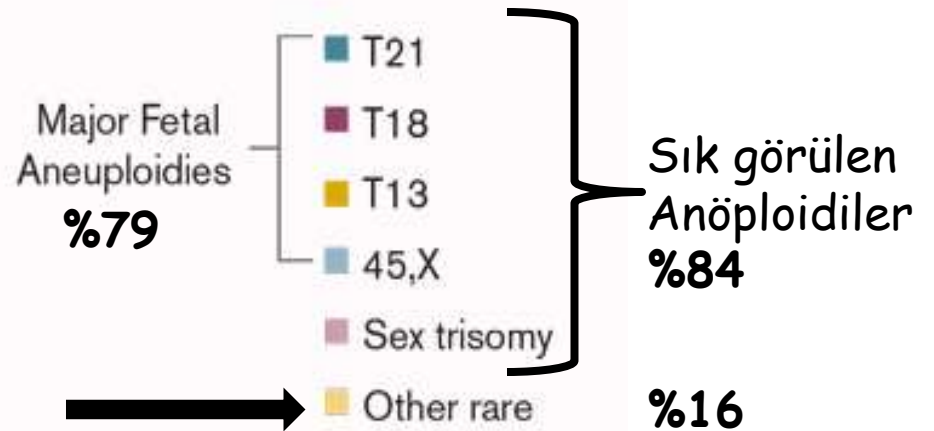
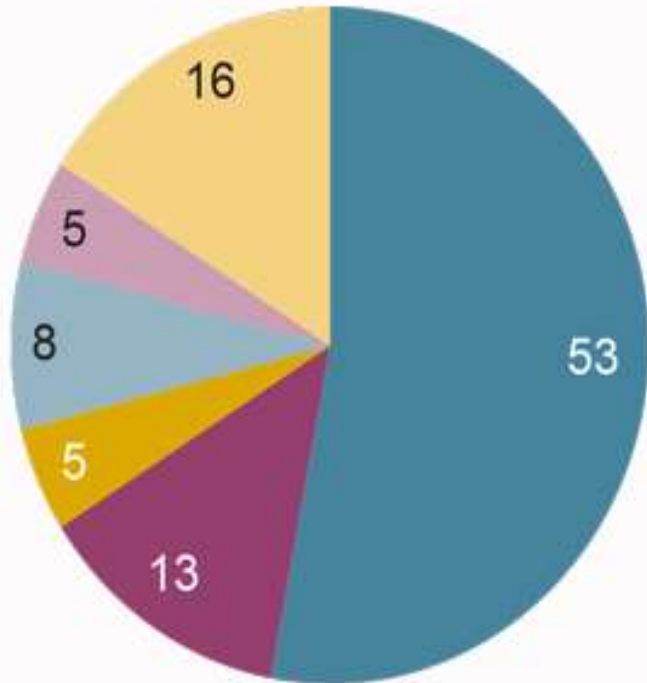
**PTPN11 dizi analizi;** 13. ekzonda heterozigot c.1529A>C de novo  
(Leopard sendromu'nda tanımlanmış bir mutasyon)

# Kromozom Anomalileri

- Yeni doğan sıklığı 1:156 (Karyotip analizi ile)
- Gebelik haftası ilerledikçe azalır
- Trizomi riski, anne yaşı ile artar
- Monozomi X riski her gebede aynıdır (postzigotik)
- Dengesiz kromozom anomalileri=fenotip etkilenir.
  - Majör kromozom anomalileri (T18, T13, T21, 3n, 45,X vd)
  - Minör kromozom anomalileri (47,XXX, 47,XXY, 47,XYY, vd)
- Dengeli kromozom anomalileri=fenotip genellikle normal (*de novo*?)



Figure 1. Prenatal Prevalence of Chromosomal Abnormalities



Data adapted from Wellesley, D. et al.<sup>2</sup>, Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe. *Eur J of Hum Gen*, 11 January 2012.

# Kromozom anomalilerinin prenatal "TANISI"

## TANI Testleri

İnvaziv Girişim (AS, CVS, KS) sonrası

- fetal kromozom analizi (Gold standart) (tüm genom)
- FISH/QF-PCR (sık görülen anöploidiler ve hedefli mikrodelsiyonlar)
- mikroarray/a-CGH (tüm genom submikroskopik anomaliler)

Kime invaziv girişim ve tanı uygulanır?



İnvaziv girişim riski 1:200

Hastalık riski 1:200

- 35 yaş anne adayının doğumda kromozom anomalili çocuk riski

# İnvaziv Girişim Endikasyonu "İleri anne yaşı"

≥35 yaş

tüm gebelerin %10'u

≥37 yaş

tüm gebelerin %5'i risk grubu

ve tümüne fetal karyotip yapılsa bile

"Tri 21 lerin %30'u saptanabilir,

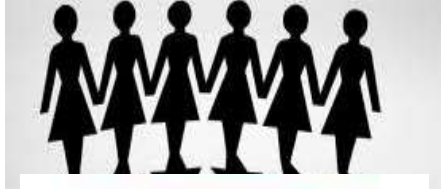
çünkü, Tri 21 lerin

%70 i <35 yaş annelerden doğar. "

**Amaç;** Daha az girişim ile daha geniş bir popülasyona ulaşmak ve daha fazla anomali yakalamak.

**"TARAMA TESTLERİ "**

# TARAMA Testleri



“Tri 21 prevalansı 1:700 →100 Tri 21 →70 000 gebelik”

**Trizomi 21**  
“yakalanacak” “doğacak”

Anne yaşı (>35)	% 10	7 000 AS	<b>30</b>	70
Üçlü test	% 5	3 500 AS	<b>60</b>	40
NT	% 5	3 500 AS	<b>75</b>	25
1. Trim. tarama	% 4,2	2 940 AS	<b>85</b>	15
Sequential	%4,2	2 940 AS	<b>90-95</b>	5-10



Trizomi 21



İzole NT (1. Trimester-CVS), izole EP (2. Trimester-AS) veya ek diğer USG bulgularının varlığında saptanan anomaliler ve oranları (2010-2014/8) (İTF, TG ABD)

**Sık görülen anöploidiler**

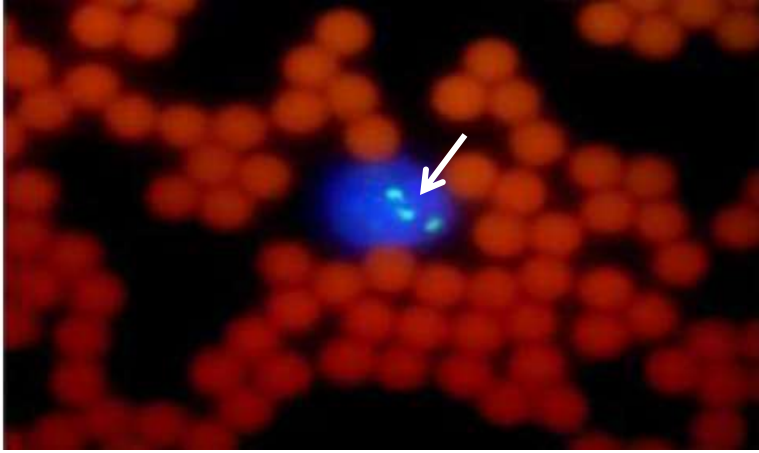
**Ender görülen anomaliler**

	T21 %	T18 %	T13 %	45,X %	Poli X/Y%	Diğer Otoz. Tri %	Dengesiz Yapısal %	Dengeli Yapısal %	Toplam %
CVS-NT	23	4,6	1,3	2	0,7	0,7	0	2,6	34,9
CVS-NT+ Diğer USG	20,7	13,8	4,8	11	0,7	2,1	3,5	0	56,6
AS-EP	1,33	0	0	0	0	0	0	1,33	2,7
AS-EP+ Diğer USG	17,2	0,9	0	1,7	0,9	0,9	1,7	0	23,3

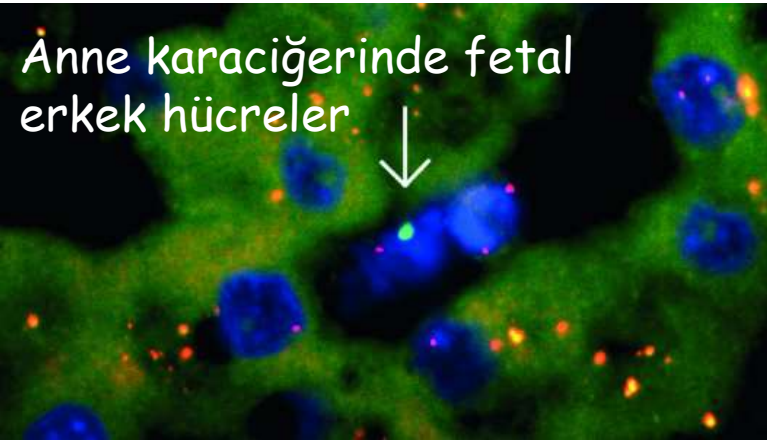
%58,6

%12,8

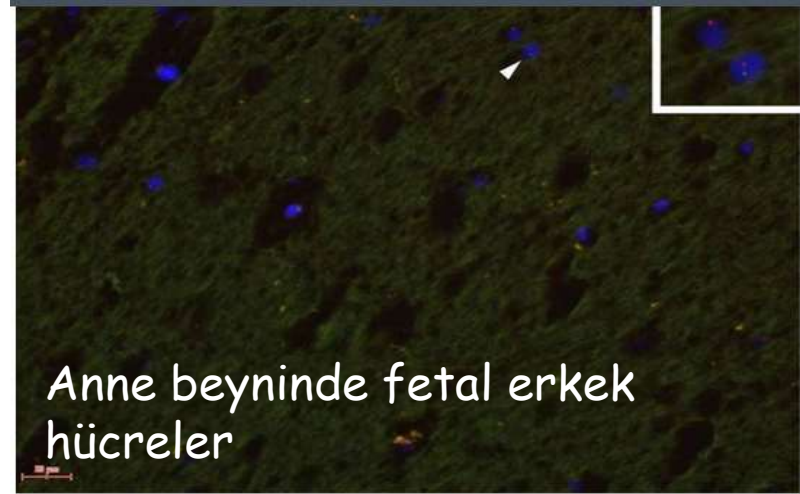
# 80'ler ve 90'lar Maternal Kanda Fetal Kromozom Anomalilerinin Tanısı için fetal hücre avı ile geçti....



Anne kan dolaşımında fetal hücreler (T21)  
1:1 000 000



Anne karaciğerinde fetal erkek hücreler



Anne beyinde fetal erkek hücreler

For the first time, scientists have found male fetal cells (shown here) in a mother's brain, as reported online Sept. 26, 2012, in the journal PLoS ONE.  
Credit: PLoS ONE 7(9): e45592. doi:10.1371/journal.pone.0045592View full size image

# PLAZMADA EKSTRASELLÜLER DNA

- 1940 larda plazmada ekstraselluler DNA'nın varlığı bildirildi,
- 1990 larda kanser hastalarının plazmalarından elde edilen serbest DNA da tümör kökenli genetik markerler saptandı,
- 1997 de erkek fetus taşıyan gebelerin plazmalarında fetusun Y kromozomuna ait markerler gösterildi (Lo et al., 1997).

## Noninvasive testing for fetal aneuploidy using fetal nucleic acids

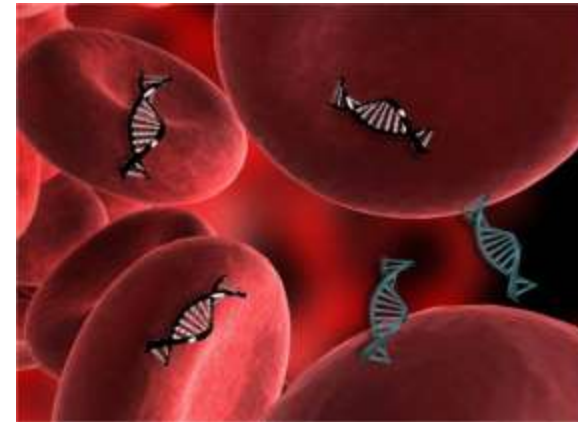
THE LANCET

Early report

### Presence of fetal DNA in maternal plasma and serum

Y M Dennis Lo, Noemi Corbetta, Paul F Chamberlain, Vik Rai, Ian L Sargent, Christopher W G Redman, James S Waincoat

1997



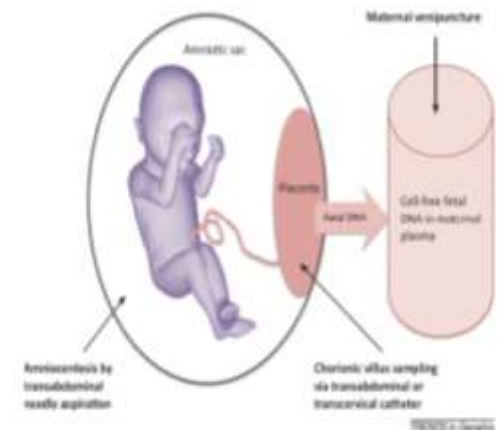
BMJ

RESEARCH

### Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study

Rossa W K Chiu, professor,<sup>1</sup> Rajat Akolekar, clinical research fellow,<sup>1</sup> Yanni W L Zheng, student,<sup>1</sup> Tak Y Leung, professor,<sup>2</sup> Hao Sun, assistant professor,<sup>1</sup> K C Allen Chan, associate professor,<sup>1</sup> Fiona M F Lun, postdoctoral fellow,<sup>1</sup> Atte T J J Go, professor,<sup>3</sup> Elizabeth T Lau, department manager and honorary assistant professor,<sup>3</sup> William W K To, consultant,<sup>4</sup> Wing C Leung, consultant,<sup>2</sup> Rebecca Y K Tang, consultant,<sup>5</sup> Sidney K C Au-Yang, consultant,<sup>6</sup> Helena Lam, consultant,<sup>6</sup> Yu Y Kung, obstetrician,<sup>6</sup> Xiaojing Zhang, manager,<sup>10</sup> John M G van Vugt, professor,<sup>4</sup> Ryoko Mirekawa, postdoctoral fellow,<sup>2</sup> Mary H Y Tang, consultant and honorary clinical associate professor,<sup>5</sup> Jun Wang, professor,<sup>6</sup> associate director,<sup>11</sup> Cees B M Oudejans, associate professor,<sup>4</sup> Tze K Lau, professor,<sup>2</sup> Kypros H Nicolaides, professor,<sup>3</sup> Y M Dennis Lo, professor<sup>10</sup>

2011

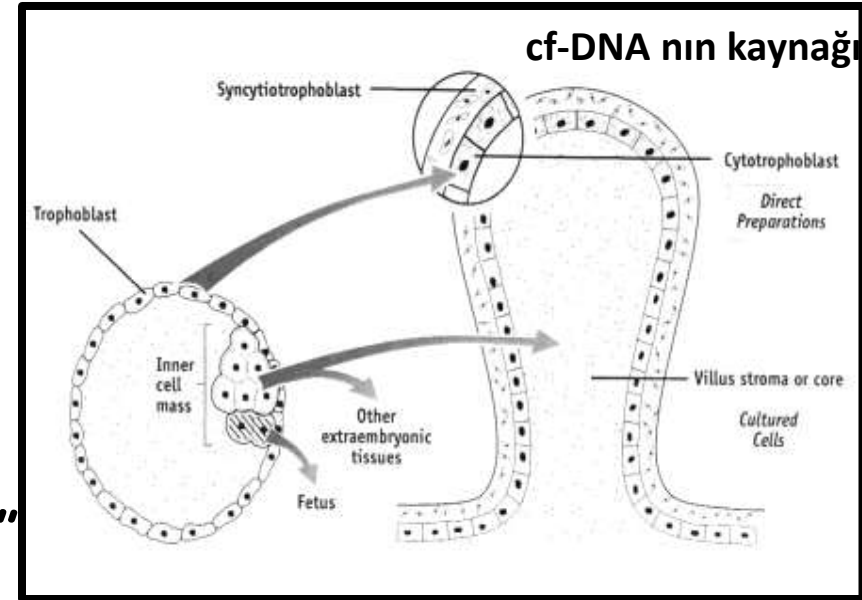


# Maternal Plazmada Dolaşan cell free DNA'nın (cf-DNA) Biyolojik Özellikleri

- Serbest dolaşımdaki cf-DNA'nın % 80'i <200 bp ve plazmadaki tüm DNA'nın % 3-10 plasenta (sitotrofoblast) kaynaklıdır,
- Implantasyonu takip eden 18 inci günden itibaren plazmada saptanmaya başlanır ve gebelik ilerledikçe miktarı artar,
- Gebelik bittikten sonra, yarı ömrü 16 dakikadır,
- Genel görüş, cf-DNA nın kalıcı olmadığıdır; ancak bir yayın fetal DNA nın uzun süre (27 yıl) maternal kanda saptanabildiğini ve bu bazı fetal hücrelerin maternal kanda uzun yaşadığı ve plazma ayrıştırması esnasında tüm nükleuslu hücrelerin iyi uzaklaştırılmaması ile açıklanmaktadır.

"cf-DNA, ağırlıklı olarak plasenta kaynaklı olduğundan, plasentaya ait özellikleri (plasenta ile sınırlı mozaisizm, plasental epigenetik özellikler, vs) yansıtmaktadır ve bu nedenle

**cfp-DNA ya da cf-DNA** olarak adlandırılması önerilmektedir."



# Fetal tests spur legal battle

*A newborn industry based on non-invasive genetic testing turns combative.*

**14 OCTOBER 2005** Sequenom licenses a patent for non-invasive prenatal diagnosis.

**10 AUGUST 2010** Sequenom's lawyers send Verinata Health a letter warning that Verinata is developing tests that will infringe on Sequenom's patent and patent application.

**30 AUGUST 2011** Stephen Quake — founder of Verinata — and Hei-Mun Fan, both at Stanford University in California, are issued a patent for 'Determination of fetal aneuploidies by massively parallel DNA sequencing'.

**17 OCTOBER 2011** Sequenom launches the MaterniT21 test.

**6 DECEMBER 2011** Sequenom sends Aria Diagnostics a letter warning about patent infringement.

**19 DECEMBER 2011** Aria files a complaint against Sequenom.

**6 JANUARY 2012** Natera files a complaint against Sequenom.

**24 JANUARY 2012** Sequenom sues Aria.

**22 FEBRUARY 2012** Verinata and Stanford University sue Sequenom.

**1 MARCH 2012** Verinata launches the Verifi prenatal test.

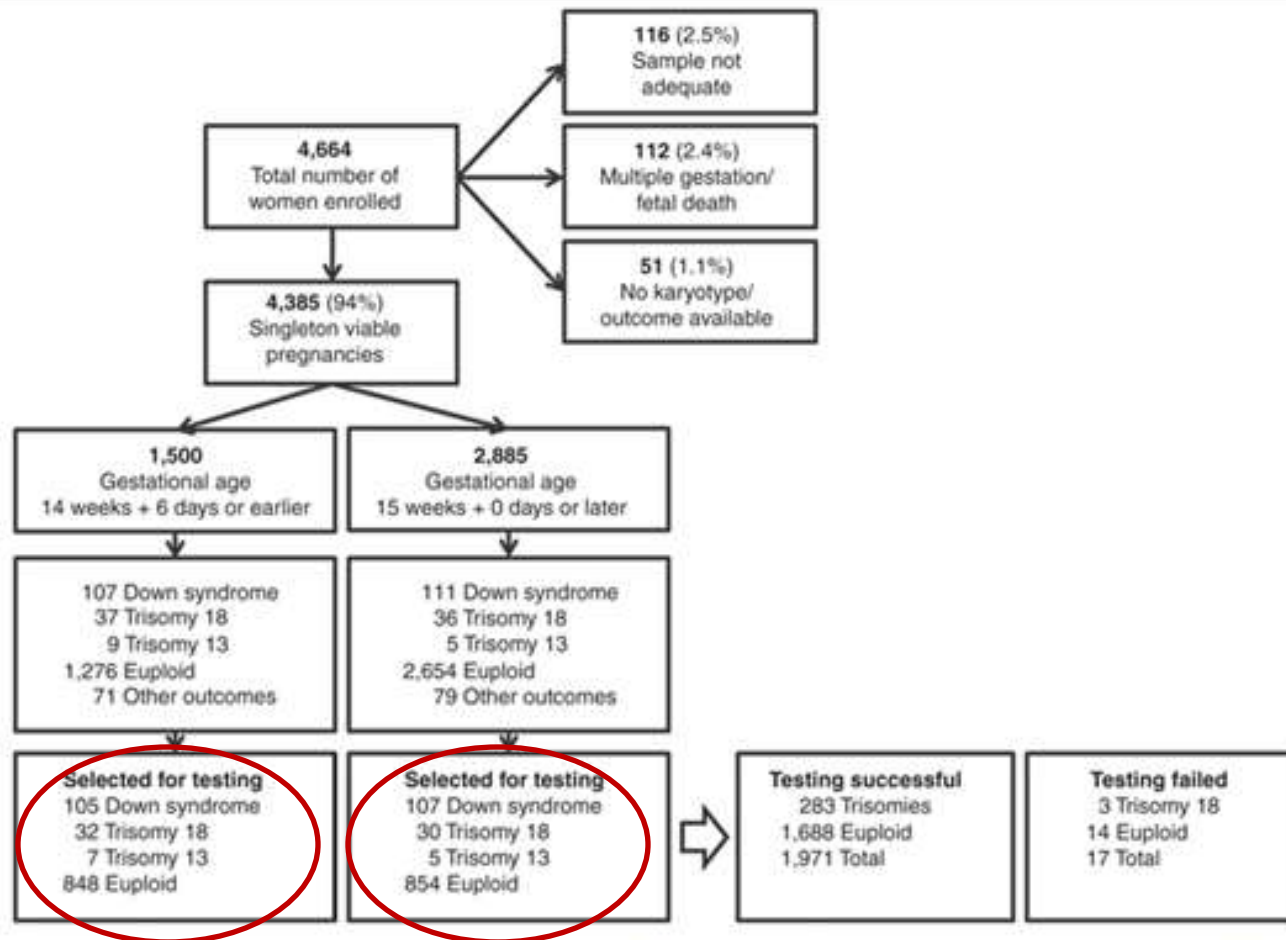
**7 MAY 2012** Ariosa (formerly Aria) launches the Harmony prenatal test.



# DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study

Glenn E. Palomaki PhD, Cosmin Deciu MS, Edward M. Kloza MS, GERALYN M. Lambert-Messerlian PhD, James E. Haddow MD, Louis M. Neveux BA, Mathias Ehrich MD, Dirk van den Boom PhD, Allan T. Bombard MD, MBA, Wayne W. Grody MD, PhD, Stanley F. Nelson MD & Jacob A. Canick PhD

*Genetics in Medicine* (2012) 14, 296–305 | doi:10.1038/gim.2011.73



Flow chart showing the cohort of samples collected, those selected for testing, and the numbers for which testing was successful. This report focuses on 1,968 pregnancies subject to testing. Of these, 286 were common trisomies (Down syndrome, trisomy 18, and trisomy 13), along with 1,702 matched euploid controls.

<b>Firma</b> <b>Son yayın</b>	<b>Sequenom</b> <b>Palomaki, 2011</b> <b>ve 2012</b>	<b>Verinata</b> <b>Bianchi,</b> <b>2012, 2014</b>	<b>Ariosa</b> <b>Norton, 2012</b> <b>Nicolaides,</b> <b>2012</b>	<b>Natera</b> <b>Zimmermann,</b> <b>2012</b> <b>Nicolaides,</b> <b>2013</b>	<b>BGI</b> <b>Jiang, 2012</b>
<b>Test adı</b>	Materni21/plus	Verifi	Harmony	Panorama	NIFTY
<b>Teknik</b>	MP shotgun S	MPSS	DANSR- targeted	NGS –SNP targeted	MPSS
<b>Hedef Anomaliler</b>	21, 18, 13, X, Y Plus + (bazı mikrodél)	21, 18, 13, X, Y	21, 18, 13 X, Y	21, 18, 13, X, Y, triploidi	21, 18, 13, X, Y
<b>Olgu sayısı</b>	1971	532/1914	3080	185	903
<b>Duyarlılığı</b>	T21 %99,1 T18 >%99,9 T13 %91,7 X/Y %96,2	T21 %100 T18 %97,2 T13 %78,6 X, Y %93,8-100	T21 %100 T18 %97,4 T13 %80	T21 >%99 T18 >%99 T13 >%99 45,X %91,7	T21 %100 T18 %100 T13 %100 45,X %75
<b>Özgüllüğü</b>	T21 %99,9 T18 >%99,6 T13 %99,7 X/Y %99,7	T21 %100 T18 %100 T13 %100 X, Y %99,6-100	T21 %99,97 T18 %99,93 T13 >%99	Tümü %100	T21 %100 T18 %99,7 T13 %100
<b>Yanlış negatif</b>	<b>T21 3/212</b> <b>T13 1/12</b> <b>X/Y 1/26</b>	<b>T18 1/36</b> <b>T13 3/14</b> <b>XX 1/233</b>	<b>T18 1/38</b> <b>T13 2/10</b>	<b>45,X 1/12</b>	<b>45,X 1/4</b>
<b>Yanlış pozitif</b>	<b>T21, T18, T13</b> <b>24/1688 ( %1,4)</b>	<b>T21 6/1909</b> <b>T18 3/1905</b>	<b>T21 1/2888</b> <b>T18 2/2888</b> <b>T13 1/1939</b>	<b>0</b>	<b>T18 1/891</b>



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



The Society for  
Maternal-Fetal Medicine

# COMMITTEE OPINION

Number 545 • December 2012

The American College of Obstetricians and Gynecologists Committee on Genetics  
The Society for Maternal-Fetal Medicine Publications Committee

*This document reflects emerging clinical and scientific advances as of the date issued and is subject to change.  
The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

## cf-DNA Endikasyonları;

- İleri anne yaşı ( $\geq 35$ )
- Fetal USG de anöploidi riskini arttıran bulgu varsa!!
- Trizomili gebelik öyküsü
- MS- tarama testlerinde trizomi için artmış risk
- 21 ve 13. kromozomlarının katıldığı Robertson tipi translokasyon için taşıyıcı ebeveynlerin gebelikleri



2013

## ACMG statement on noninvasive prenatal screening for fetal aneuploidy

Anthony R. Gregg, MD<sup>1</sup>, S.J. Gross, MD<sup>2</sup>, R.G. Best, PhD<sup>3</sup>, K.G. Monaghan, PhD<sup>4</sup>, K. Bajaj, MD<sup>2</sup>, B.G. Skotko, MD<sup>5</sup>, B.H. Thompson, MD<sup>6</sup> and M.S. Watson, PhD<sup>6</sup>; are The Noninvasive Prenatal Screening Work Group of the American College of Medical Genetics and Genomics

### WHAT ARE THE CURRENT LIMITATIONS OF NIPS?

1. Risk assessment is limited to specific fetal aneuploidies (trisomy 13, 18, and 21) at this time. Some platforms also screen for sex chromosome abnormalities. Approximately 50% of cytogenetic abnormalities routinely identified by amniocentesis will not be detected when trisomy 21, 18, and 13 are the only aneuploidies being screened. When patients <35 years or >35 years are considered separately, 75 and 43% of cytogenetic abnormalities will be missed, respectively.<sup>11,12</sup>
2. Chromosomal abnormalities such as unbalanced translocations, deletions, and duplications will not be detected by NIPS. Therefore, when fetal anomalies are detected, invasive diagnostic testing and cytogenomic microarray analysis are more likely to detect chromosomal imbalances than NIPS and may be a better testing option.<sup>13</sup>
3. NIPS is not able to distinguish specific forms of aneuploidy. For example, NIPS cannot determine if Down syndrome is due to the presence of an extra chromosome (trisomy 21), a Robertsonian translocation involving chromosome 21, or high-level mosaicism. Identification of the mechanism of aneuploidy is important for recurrence risk counseling and emphasizes the importance of diagnostic testing following NIPS.
4. NIPS does not screen for single-gene mutations.
5. Uninformative test results due to insufficient isolation of cell-free fetal DNA could lead to a delay in diagnosis or eliminate the availability of information for risk assessment. Biologic factors associated with reduced available cell-free fetal DNA include a high body mass index and early gestational age (<10 weeks gestation).<sup>14,15</sup>
6. Currently, it takes longer for NIPS test results to be returned than for test results on maternal serum analytes. Providers should keep this in mind when offering patients NIPS if timing is important for reproductive decision making. In

- 1-2. Risk değerlendirmesi T21, T18 ve T13 ile sınırlı (bazıları X ve Y için de tarama yapıyor). Eğer tarama bu üç trizomi için yapılırsa **AS ile saptanabilecek anomalilerin ~%50 si (<35 yaş gebelerde bu oran %75 ve >35 yaş gebelerde %43) yakalanamayacaktır** (diğer trizomiler, yapısal anomaliler, mozaikler ve aCGH ile tanınabilecek anomaliler).
3. Trizomilerin translokasyon tipi olup olmadığı genetik danışma için önemlidir bu yüzden NIPS de trizomi saptanırsa kromozom analizi önemlidir.
4. NIPS tek gen mutasyonlarını taramaz.
- 5-6. NIPS başarısız olabilir, bu da tanının gecikmesine yol açar.
7. NTD-AFP
8. NIPS, 1. trimester USG nin kazançlarını karşılamaz.

## SHOULD PRETEST OR POSTTEST GENETIC COUNSELING ABOUT ANEUPLOIDY SCREENING BE PERFORMED?

Pretest information should be provided by a prenatal care provider, a trained designee, or a genetic counselor to ensure patients make informed decisions. Aneuploidy screening is not a routine prenatal test; it is acceptable for patients to decline screening.

Pretest information should include:

1. A brief explanation of the purpose of NIPS.
2. Advantages of NIPS as compared with maternal serum analyte screening.
  - On the basis of available data, detection rates appear to be higher.
  - There is a high negative predictive value for Down syndrome. This may be important for patients seeking to avoid the risks (e.g., fetal loss) inherent with invasive testing.
  - NIPS has a lower false-positive rate, meaning fewer women will receive a "positive" screen, necessitating fewer invasive procedures.
  - Risk assessment is less dependent on gestational age.
3. Considerations for follow-up invasive testing if NIPS indicates an increased risk for aneuploidy.
4. Limitations of NIPS.

Posttest counseling is recommended when NIPS indicates that a patient is at high risk or has a "screen-positive" result. When a "screen-negative" result is encountered, residual

Test öncesi danışma şunları içermeli;

1. NIPS in amacı kısaca açıklanmalı,
2. Diğer anne kanı tarama testlerine karşı avantajları
  1. Eldeki bilgi birikimi ile yakalama oranı daha yüksek
  2. Negatif prediktif değer yüksek ve
  3. Yanlış pozitiflik oranı daha az dolayısıyla **daha az girişim**
  4. Risk hesaplaması gebelik haftasından bağımsız
3. Eğer NIPS pozitif ise invaziv girişim,
4. NIPS 'in limitleri (Yanlış negatifler, CPM, diğer kromozom anomalileri, vd)

## Opinion

### Non-invasive prenatal diagnosis for Down syndrome: the paradigm will shift, but slowly

P. Benn<sup>\*†</sup>, H. Cuckle<sup>‡</sup> and E. Pergament<sup>§</sup>

1. Down sendromu için "tanı" mı yoksa tarama mı?  
NIPT çok yüksek duyarlılığı olan TARAMA testidir,
2. Tarama testi + ise, NIPT invaziv prenatal tanının yerini alabilir mi?  
Diğer tarama testi + ve NIPT+ ise Down sendromu riski 290 kez artmıştır,  
NIPT - ise risk 110 kez azalmıştır ancak "rezidual risk" önemli ve ciddidir,
3. Fetal kromozom analizinde (CVS ve AS) saptanan diğer anöploidileri saptayabilir mi?  
T21 anomalilerin yarısını oluşturur, tarama testleri ile diğer anöploidi ve triploidi için risk hesaplanabilir, ancak NIPT çalışmalarında klinik süreç tamamlanmadı,
4. FISH veya mikroarray teknikleri ile saptanan mikrodelsiyon/duplikasyon sendromları?  
NIPT ile mikrodelsiyon/duplikasyon tanısının yakın gelecekte gerçekleşmesi bekleniyor,
5. Klasik tarama testlerinin yerini alır mı? Evet ise biokimyasal ve USG nin konjenital malformasyonların erken gebeliklerdeki potansiyel faydalarını kaybeder miyiz?  
USG'nin yerini alamaz.

cf-DNA özellikle non-viable trofoblast kökenli olduğundan "CPM" riskini taşır.  
NIPT testleri yüksek riskli gruplarda yapılmış ve yapılmaktadır.  
NIPT'nin düşük ve orta risk grubunda performansı daha düşüktür, buna karşın maliyeti artıracaktır.



## Noninvasive prenatal testing for aneuploidy—ready for prime time?

Lyn S. Chitty, MRCOG; Melissa Hill, PhD; Helen White, PhD; David Wright, PhD; Stephen Morris, PhD

Tarama testi > 1:150 ise  
->NIPT + ise ->CVS

1:380 Down s. Prevalansı (35 yaş)  
500 000 gebelikte 1 389 Down s.

Taramada >1:150 ise

↓  
13 646 NIPT %99 DR ve %1 FPR

↓  
1 305 CVS

↓  
13 düşük ve 1 169 Down s. → NIPT 200 £ ise → tarama+tanı 29,7 milyon £

TABLE 2  
Projected numbers undergoing noninvasive prenatal diagnosis

Screening Cut-off (1 in)	NIPD			CVS						
	DR <sub>S</sub>	FPR <sub>S</sub>	NIPD	DR <sub>N</sub>	FPR <sub>N</sub>	TP <sub>N</sub>	FP <sub>N</sub>	FN <sub>S+N</sub>	CVS	Miscarriages
150	85.0%	2.5%	13,646	99.0%	1.0%	1169	136	220	1305	13
500	94.0%	7%	37,704	99.0%	1.0%	1293	377	96	1670	17
1000	96.0%	12%	60,668	99.0%	1.0%	1320	607	69	1927	19
2000	98.0%	19%	94,103	99.0%	1.0%	1348	941	41	2289	23
5000	99.0%	31%	155,944	99.0%	1.0%	1361	1559	28	2921	29
10,000	99.5%	43%	215,785	99.0%	1.0%	1368	2158	21	3526	35

Figures calculated for hypothetical population of 500,000 women. With Down syndrome prevalence at screening of 1 in 360 number of affected fetuses is 1389. Using invasive prenatal diagnosis rather than NIPD with screening cut-off of 1 in 150, 13,646 women would undergo CVS, detecting 1181 Down syndrome prevalence cases with estimated 136 miscarriages. CVS, chorionic villus sampling; DR<sub>N</sub>, detection rate with NIPD; DR<sub>S</sub>, detection rate with screening; FN<sub>S+N</sub> combined false-negative results with screening and NIPD = number of Down syndrome prevalence cases - TP<sub>N</sub>; FP<sub>N</sub>, false-positive results with NIPD; FPR<sub>N</sub>, false-positive rate with NIPD; FPR<sub>S</sub>, false-positive rate with screening; NIPD, noninvasive prenatal diagnosis; TP<sub>N</sub>, true positives with NIPD.

Chitty. Noninvasive prenatal testing for aneuploidy. Am J Obstet Gynecol 2012.

## Noninvasive prenatal testing: limitations and unanswered questions

Monica A. Lutgendorf, MD<sup>1,\*</sup>, Katie A. Stoll, MS<sup>1</sup>, Dana M. Knutzen, MS<sup>1</sup> and Lisa M. Foglia, MD<sup>1,\*</sup>

Prior screening algorithms for aneuploidy involve ultrasound and/or serum screening in the first and/or second trimesters, with trisomy 21 detection rates of 81–96% with false-positive rates set at 5%.<sup>7</sup> Initial reports of NIPT describe detection rates of 98–99% or higher for trisomy 21, 44–91% for trisomy 13, and 83–95% for trisomy 18, with false-positive rates of 1–2%.<sup>8–11</sup> Sensitivity and specificity are high; however, the positive predictive value (reliability of a positive test) and the negative predictive value (reliability of a negative test) are affected by the prevalence of the disease in the population tested. The lower the disease prevalence, the higher the negative predictive value (true negatives) and the lower the positive predictive value (true positives). For example, with sensitivity of 100% and specificity of 99% (1 false-positive in 100), if the disease prevalence is high (risk of Down syndrome of 10 per 100, 10%), screening 1,000 patients would result in a positive predictive value of 91%. With a lower disease prevalence (risk of Down syndrome of 1 per 1,000), screening 1,000 patients would result in a positive predictive value of 9%. Therefore, the prevalence of the condition being screened for must be taken into account when interpreting test results, particularly the positive predictive value, as with a lower disease prevalence, a positive result is less reliable (more likely to be a false-positive result).

Duyarlılık %100

Özgüllük %99 ( 100' de 1 yanlış pozitif)

Prevelans Down sendromu %10 ise  
1000 olguda;

Pozitif prediktif değer **%91**

Prevelans Down sendromu %0,1 ise  
1000 olguda;

Pozitif prediktif değer **%9**

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 27, 2014

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## DNA Sequencing versus Standard Prenatal Aneuploidy Screening

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

*“The study’s endpoint was a comparison of false positive rates for trisomies 21 and 18 between the two methods. The false positive rate for combined trisomies 18 and 21 among those undergoing DNA testing was 0.45 percent while the rate for standard testing was 4.2 percent, a statistically significant difference.*

*Another comparison was made for positive predictive value of test results: DNA results for **trisomy 21 had a predictive value of 45.5 percent** compared to 4.2 percent in standard testing; DNA results for **trisomy 18 had a predictive value of 40.8 percent** compared to 8 percent for standard testing, a significant improvement.”*

# TARAMA Testleri



Tri 21 prevalansı 1:700 → 100 Tri 21 → 70 000 gebelik

## Trizomi 21

"yakalanacak" "doğacak" "fetal kayıp"  
0,5-1%

Anne yaşı (>35)	% 10	7 000 AS	<b>30</b>	70	35-70
Üçlü test	% 5	3 500 AS	<b>60</b>	40	17-35
NT	% 5	3 500 AS	<b>75</b>	25	17-35
1. Trim. Tarama	% 4,2	2 940 AS	<b>85</b>	15	15-30
Sequential	%4,2	2 940 AS	<b>90-95</b>	5-10	15-30
cf-DNA	%0,45	315 AS	<b>98</b>	2	2-3

← Hedef Trizomi 21 tanısı ise





# cf-DNA konfirmasyon sonuçları-1

Trizomi 21	Endikasyon	Karyotip	Gebelik akıbeti	Yorum
1. A86/14	PatUSG+1.TST+AY+cf-T21	47,+21	tahliye	
2. A210/13	PatUSG+1.TST+AY+cf-T21	47,+21	tahliye	
3.A218/14	PatUSG+1.TST+AY+cf-T21	47,+21	tahliye	
4. A325/14	PatUSG+AY+4'lü+cf-T21	47,+21	tahliye	
5.A209/14	PatUSG+AY+cf-T21	47,+21	tahliye	
6.A227/14	PatUSG+cf-T21	FISH 3x21		
7. T56/13	NT+cf-T21	47,+21	tahliye	
8. T7/14	NT+ cf-T21	46,der(21q;21q),+21, dn	tahliye	
9. A479/13	1.TST+AY+cf-T21	47 +21	tahliye	
10. A1/14	AY+cf-T21	47,+21	tahliye	
11. A238/13	cf-T21	47 +21	tahliye	
12. A193/14	cf-T21	46/47,+21(35/20)	tahliye	
13.A191/14	PatUSG+AY+cf normal	AS 46/ 47,+21 (2/32) I-FISH AS 10/65 KS 24/46	tahliye Plasenta I-FISH 1. Bölge 50/50 2. Bölge 147/3 3. Bölge 104/9 4. Bölge 130/20	<b>YANLIŞ NEGATİF</b> ↑ <b>GM</b>
<b>Trizomi 18</b>				
1. A218/13	PatUSG+AY+cf-T18	47,+18	tahliye	
<b>Trizomi 13</b>				
1. A92/14	1.TST+AY+cf-T13	AS N female	doğdu N	<b>YANLIŞ POZİTİF</b> Plasenta N Karyotip+FISH (145)



# cf-DNA konfirmasyon sonuçları-2

Monozomi X	Endikasyon	Karyotip	Gebelik akıbeti	Yorum
1. A30/14	cf monozomi X	45,X/46,X,i(Xq) (TS)	tahliye	
2. A2/14	AY +cf monozomi X	N female	doğdu	<b>YANLIŞ POZİTİF</b>
3. A104/14	4'lü+cf monozomi X	N female	devam	<b>YANLIŞ POZİTİF</b>
4. A137/14	AY+2'li+cf monozomi X	N female	doğdu	<b>YANLIŞ POZİTİF</b>
		Plasenta I-FISH 1-4/100 (4 bölge) ve Kordon fibro 2/98		
5. A114/14	AY+4'lü +cf monozomi X	45,X/46,XX (9/50) I-FISH 2/88	doğdu N Plasenta FISH	Karyotip
		1. Bölge X/XX/XXX	91/22/1	0/9/5
		2. Bölge	97/17/0	0/0/18
		Kordon kanı	2/111/4	8/25/0

## 47,XXY

1.A189/14	AY+cf XXY	47,XXY	devam	
2. A98/14	AY+cf XXY	N male	devam	<b>YANLIŞ POZİTİF</b>
3. A282/13	cf XXY	N male	doğdu	<b>YANLIŞ POZİTİF</b>

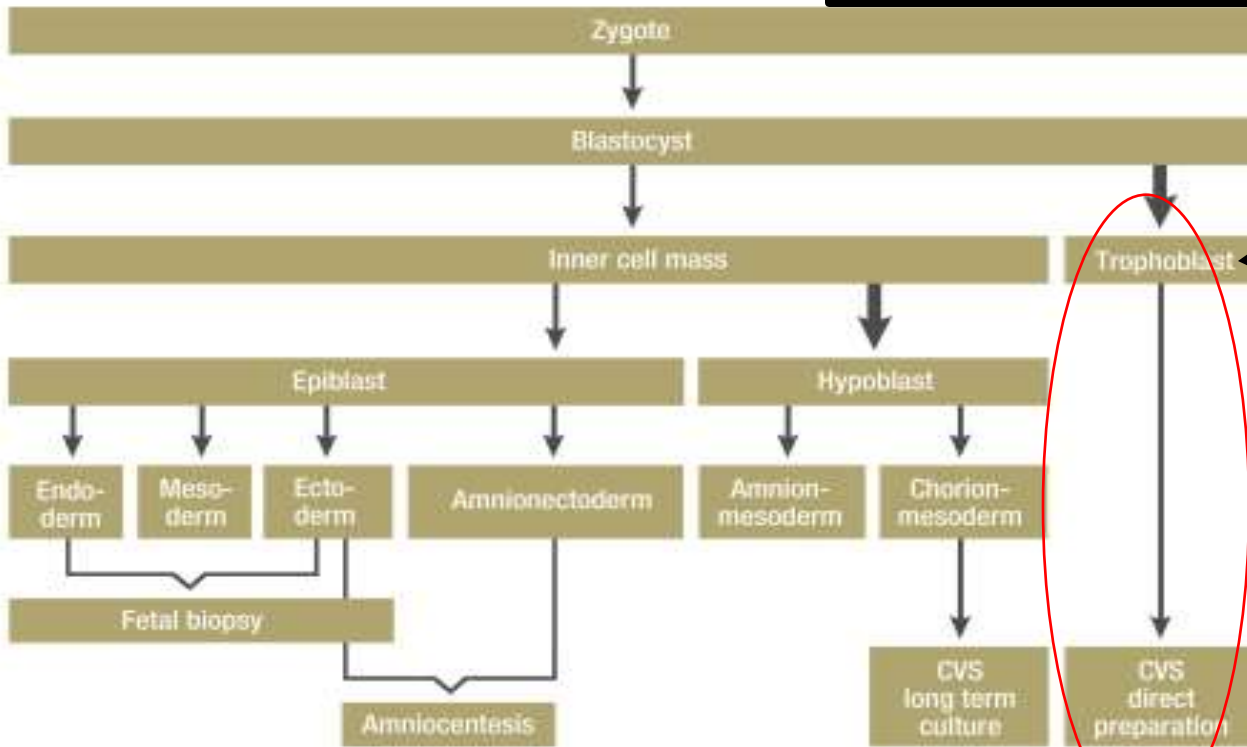
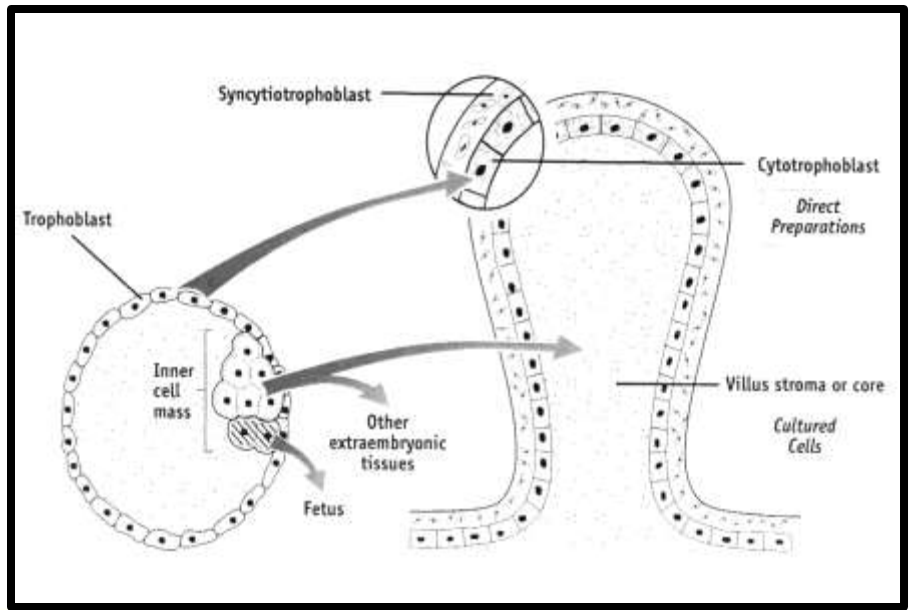
**TOPLAM 23 olgudan;  
6 sı "Yanlış pozitif"  
1 i "Yanlış negatif"  
16 sı "doğru"**

## Yapısal Kromozom Anomalisi

1.A290/13	AY+1.TST+cf DNA normal	45,XY,t(13q;14q)	doğdu	
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## cf-DNA testlerinin "yanlış pozitif" veya "yanlış negatif" sonuçlanma nedenleri;

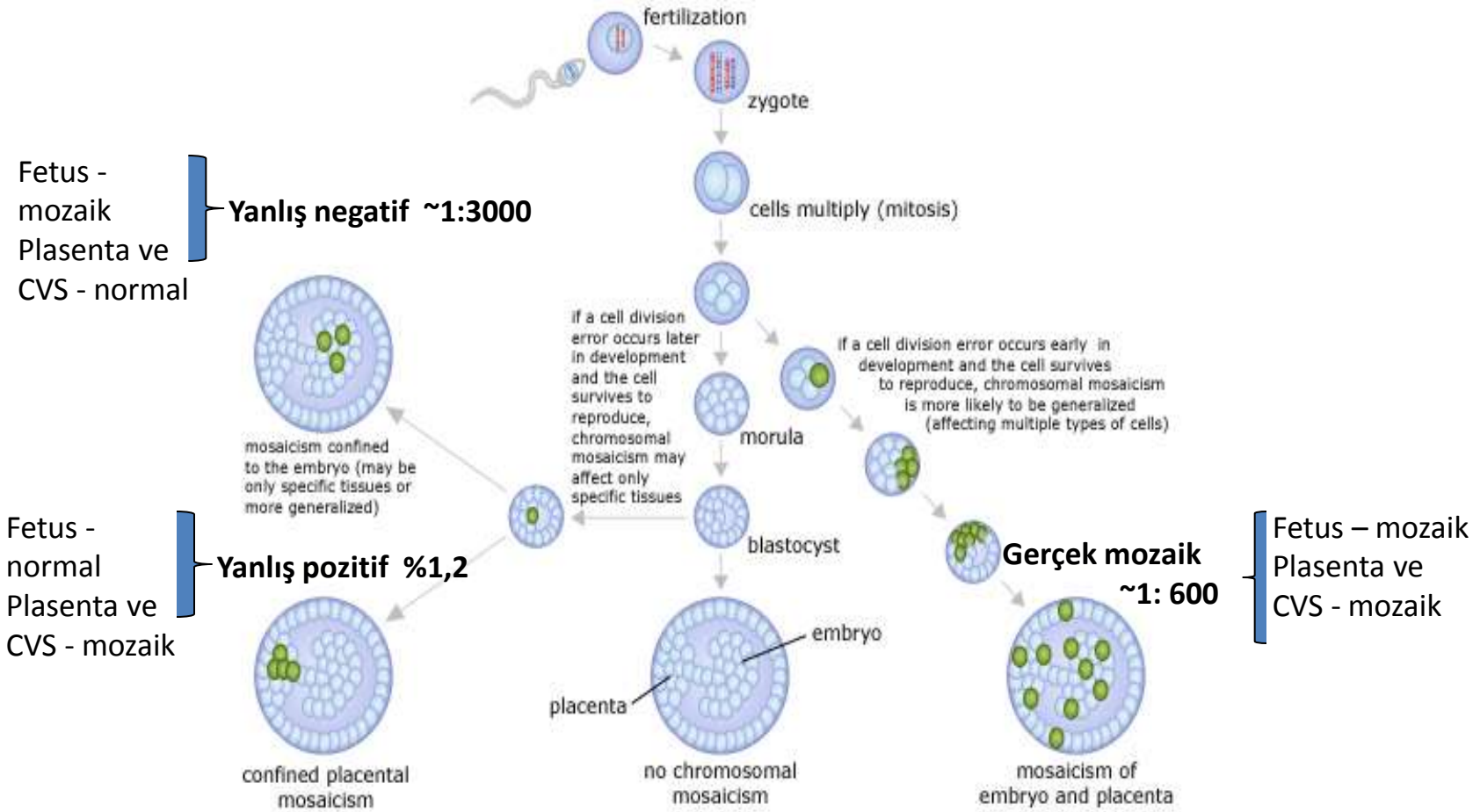
1. Plasenta ile sınırlı mozaizm
2. Gerçek düşük oranlı mozaizm
3. UPD
4. Vanishing twin
5. Maternal mozaizm
6. Maternal sorunlar (kanser, obesite, vs)
7. Teknik sorunlar



cf-DNA nın kaynağı



# PLASENTA İLE SINIRLI MOZAIKİZM



© Clinical Tools, Inc.

CPM tiplerinin sıklıkları EUCROMIC 1986-1992

48 laboratuvar n:62 865 CVS

Hahnemann JM&Vejerslev LO, 1997, Prenat Diagn:17;801

# 1989-2014/8 ay İTF-TGABD+PREMED

	Endikasyon	CVS-DP	CVS-HK	Fetal doku	Sonuç	Gebelik akıbeti
1	PatUSG	46	47,+21	yok	DP YN	IUMF
2	PatUSG	46	47,+21	AS IFISH T21	DP YN	tahliye
3	PatUSG+1.TRİ	46	47,+18	yok	DP YN	tahliye
4	1.TRİ	46 IFISH N	47,+18	AS IFISH T18	DP YN	tahliye
5	PatUSG	46 IFISH %40	47,+18	yok	DP YN	tahliye
6	PatUSG	92	47,+13/92	AS T13	DP YN	tahliye
7	PatUSG	46	47,+7	yok	DP YN	tahliye
8	PatUSG	46	46/47,+8	yok	DP YN	tahliye
9	İAY+KAÇ	46	46/47,+9	yok	DP YN	tahliye
10	PatUSG	46	46/47,+9	AS N	DP YN	tahliye
11	KAE+PatUSG	46,t(11q;22q) IFISH mos	46,t(11q;22q)/47,t(11q;22q)+9	yok	DP YN	tahliye
12	PatUSG	46	46/47,+10	yok	DP YN	tahliye
13	ÜT	46	46/47,+15	AS N	DP YN	tahliye
14	1.TRİ	46 IFISH mos	47,+16	AS IFISH mos	DP YN	tahliye
15	ÜT+İAY	46	46/47,+16	yok	DP YN	IUMF
16	PatUSG	46	69,XXX	yok	DP YN	tahliye
17	PatUSG	46	69,XXX	yok	DP YN	tahliye
18	PatUSG	46	46/46,dup(11)(p11.2p15.5)dn	46,dup(11)(p11.2p15.5)	DP YN	tahliye
19	PatUSG+1.TRİ	46	45,der(15;18)(p10;p10)dn	45,der(15;18)(p10;p10)	DP YN	tahliye
20	PatUSG+İAY	46,5p+	46,del(5)(p13.3->pter)dn	46,del(5)(p13.3->pter)	DP YN	tahliye
21	1.TRİ	47,+16	üreme yok	AS 46/47+16	GM	tahliye
22	PatUSG+İAY	46/47,+18	47,+18	yok	GM	tahliye
23	PatUSG+1.TRİ	4n	2n/4n	yok	GM	tahliye
24	PatUSG	2n/4n	2n/4n	yok	GM	tahliye
25	PatUSG+1.TRİ	46/47,+idic(14/22)	46/47,+idic(14/22)	yok	GM	doğdu
26	PatUSG+İAY	47,+22	46	yok	HK YN?	tahliye

**CVS "DP-Yanlış Negatif" (cf-DNA "yanlış negatif" olacak)**

## 1989-2014/8 ay İTF-TGABD+PREMED

	Endikasyon	CVS-DP	CVS-HK	Fetal doku	Sonuç	Gebelik akıbeti
1	PatUSG	46	47, +21	yok	DP YN	IUMF
2	PatUSG	46	47, +21	AS IFISH T21	DP YN	tahliye
3	PatUSG+1.TRİ	46	47, +18	yok	DP YN	tahliye
4	1.TRİ	46 IFISH N	47, +18	AS IFISH T18	DP YN	tahliye
5	PatUSG	46 IFISH %40	47, +18	yok	DP YN	tahliye
6	PatUSG	92	47, +13/92	AS T13	DP YN	tahliye

**CVS "DP-Yanlış Negatif" (cf-DNA "yanlış negatif" olacak)**

**T21 2/195 ~1:98**

**T18 3/90 ~1:30**

**T13 1/39 ~1:39**

# 1989-2014/8 ay İTF-TGABD+PREMED

## Fetal dokuda konfirme edilemeyen "Yanlış Pozitif" CVS olguları:

	Endikasyon	CVS-DP	CVS-HK	Fetal doku	Sonuç	Gebelik akibeti
1	1.TRİ+İAY	48,+7,+2/47,+2	46/47,+2	AS 46,XX	CPM DP-YP T7 GM T2	devam
2	PatUSG	48,+7,+18/47,+18	47,+18	yok	CPM DP-YP	tahliye
3	PatUSG	48,+18,+20/ 47,+18/47,+20	47,+18	F. deri 47,XX,+18	CPM DP-YP	tahliye
4	PatUSG	47,XX,+20	45,X/46,XX	AS 45,X/46,XX	CPM DP-YP T20 YN 45,X	tahliye
5	İAY+TG	46/47,+18	46	AS 46	CPM DP-YP	?
6	1.TRİ	46/47,+3	46	46	CPM DP-YP	devam
7	PatUSG+ICSI	46/46,t(2q;4q)	46	yok	CPM DP-YP	devam
8	İAY+TG	46/48,+mar,+mar	46	AS 46	CPM DP-YP	devam
9	PatUSG+KOÖ	46,1q-	46	KS N	CPM DP-YP	devam
10	İAY	47,+21	47,+21/48,+21,+10	47+21	CPM HK-YP	tahliye
11	KAÇ	yok	46/47,+10	AS 46	CPM HK-YP	devam
12	1.TRİ+ICSI	46	46/47,+2	yok	CPM HK-YP	devam
13	TG	46	46/47,+2	yok	CPM HK-YP	devam
14	PatUSG+İAY+ ICSI	46	46/46,11q+	AS 46	CPM HK-YP	devam

CVS "DP-Yanlış Pozitif" (cf-DNA "yanlış pozitif olacak")

14/3090 %0,45 yani 1:221



# 1989-2014/8 ay İTF-TGABD+PREMED

Mozaik X anöloidileri n: 15 15/3090

%0,5 yani 1:206

	Endikasyon	CVS-DP	CVS-HK	Fetal doku	Sonuç	Gebelik akıbeti
1	İAY	yok	45,X	AS 47,XXX	GM	doğdu
2	PatUSG	45,X	45,X/46,XX	yok	GM	tahliye
3	PatUSG	45,X/47,XXX	45,X/47,XXX	yok	GM	tahliye
4	1.TRİ	45,X	45,X/47,XXX	yok	GM	devam
5	1.TRİ	45,X/47,XXX	45,X/47,XXX	AS 45,X/46,XX/47,XXX	GM	tahliye
6	PatUSG	45,X	45,X/46,XXq-	yok	GM	tahliye
7	PatUSG	45,X/46,XX/47,XXX	45,X/46,XX/47,XXX	yok	GM	tahliye
8	1.TRİ	45,X I-FISH XY	45,X/46,XY	AS 45,X/46,XY	GM	?
9	1.TRİ+PatUSG	45,X I-FISH XY	45,X/46,XY I-FISH XY	AS 45,X/46,XY	GM	?
10	PatUSG	46,XX	45,X	yok	GM DP YN	tahliye
11	PatUSG	47,XXX I-FISH XXX	45,X	yok	GM DP YN	tahliye
12	PatUSG	46,X,r(X)	45,X	yok	GM DP YN	tahliye
13	PatUSG	45,X/46,XX	46,XX	KS 46,XX	CPM DP-YP	devam
14	İAY+ICSI	47,XXY	46,XY	yok	CPM DP-YP	devam
15	1.TRİ	46,X,r(X)	46,XX	AS 46,XX	CPM DP-YP	devam

**Sonuç: Tüm CVS serisinde tüm kromozom anomalileri için**

**DP-YN 23/3090 (cf yanlış negatif) %0,74 ~1:135**

**DP-YP 12/3090 (cf yanlış pozitif) %0,39 ~1:256**



1989-2011 CVS ve AS serilerinde olguların ana endikasyon gruplarına göre dağılımı ve bu gruplarda saptanan anomali oranları (İTF-TGABD+PREMED)

Girişim endikasyonu	CVS Serisi			AS Serisi		
	$\Sigma n$	n ano	ano %	$\Sigma n$	n ano	ano %
Parental kro.anomalisi	101	59	58,4	136	126	55,9
Diğer (<1:200)	841	10	1,2	625	6	1
Düşük risk (%1-1,4)	55	4	7,3	956	12	1,3
<b>İleri anne yaşı</b>	335	<b>16</b>	<b>4,8</b>	10430	<b>232</b>	<b>2,2</b>
<b>Tarama testi</b>	282	<b>53</b>	<b>18,8</b>	6749	<b>186</b>	<b>2,8</b>
<b>Pat-USG</b>	824	<b>245</b>	<b>28,7</b>	4442	<b>376</b>	<b>8,5</b>
toplam	2453	<b>387</b>	15,8	22813	<b>889</b>	3,9

CVS serisinin farklı endikasyonlarında saptanan anomalilerde cf-DNA testinin etkinliği (cf-DNA'nın %100 yakalama oranı olsaydı)(İTF-TGABD+PREMED, 1989-2011),

		Cf-DNA 😊			Cf-DNA 😞									
CVS Endikasyon n:2453	Toplam kromozom anomalisi		Sık görülen anöplidiler (21, 18, 13, X ve Y)			Rezidual Riskler (Diğer kromozom anomalileri)								
						Toplam risk			Dengeli anomaliler			Dengesiz anomaliler		
Σn	n	%	n	%	risk	Σn	%	risk	n	%	risk	n	%	risk
Diğer n:841	10	1,2	3	0,4	1:250	7	0,8	1:12	5	0,6	1:167	2	0,2	1:500
Düşük risk n:55	4	7,3	2	3,6	1:28	2	3,6	1:28	1	1,8	1:56	1	1,8	1:56
İAY n:335	15	4,5	12	3,6	1:28	3	0,9	1:111	2	0,6	1:167	1	0,3	1:333
ST n:282	53	18,8	39	13,8	1:7	14	5	1:20	1	0,4	1:250	13	4,6	1:22
P-USG n:824	244	29,6	204	24,8	1:4	40	4,9	1:20	7	0,9	1:111	33	4	1:25
KAE n:101	59	58,4	8	7,9	1:13	51	50,5	1:2	35	34,7	1:3	16	15,8	1:6

# "cf-DNA Tarama Testi"

1. Test öncesi genetik danışma önemlidir.
2. Aile öyküsü alınmalı ve gebelikte prenatal tanısı mümkün diğer genetik hastalıklar için risk olup olmadığı belirlenmeli ve bu testin YP ve YN sonuçları ile diğer kromozom anomalileri için kalan risk anlatılmalıdır
3. cf-DNA testi rutin prenatal laboratuvar uygulamalarının bir parçası olmamalı, test hasta seçimine bırakılmalıdır.
4. Eğer fetal USG de herhangi bir anomali saptanırsa invaziv prenatal tanı önerilmelidir.
5. cf-DNA testi sonucu "**pozitif**" ise genetik danışma ve konfirmasyon amacı ile invaziv prenatal tanı önerilmelidir.
6. cf-DNA test sonucu "**normal**" ise genetik danışma daha da önemli ve USG ile takip önerilmelidir.
7. cf-DNA testi, CVS veya amniosentezin tanısının güvenilirliğini ve doğruluğunu karşılayamaz.

.....coming soon .....

www.ScienceTranslationalMedicine.org 6 June 2012 Vol 4 Issue 137 137ra76

RESEARCH ARTICLE

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GENOMICS

## Noninvasive Whole-Genome Sequencing of a Human Fetus

Jacob O. Kitzman,<sup>1\*</sup> Matthew W. Snyder,<sup>1</sup> Mario Ventura,<sup>1,2</sup> Alexandra P. Lewis,<sup>1</sup> Ruolan Qiu,<sup>1</sup> LaVone E. Simmons,<sup>3</sup> Hilary S. Gammill,<sup>3,4</sup> Craig E. Rubens,<sup>5,6</sup> Donna A. Santillan,<sup>7</sup> Jeffrey C. Murray,<sup>8</sup> Holly K. Tabor,<sup>5,9</sup> Michael J. Bamshad,<sup>1,5</sup> Evan E. Eichler,<sup>1,10</sup> Jay Shendure<sup>1\*</sup>

ARTICLE

320 | NATURE | VOL 487 | 19 JULY 2012

doi:10.1038/nature11251

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## Non-invasive prenatal measurement of the fetal genome

H. Christina Fan<sup>1†\*</sup>, Wei Gu<sup>1\*</sup>, Jianbin Wang<sup>1</sup>, Yair J. Blumenfeld<sup>2</sup>, Yasser Y. El-Sayed<sup>2</sup> & Stephen R. Quake<sup>1,3,4</sup>

**Prenatal Tani?**



# cf-DNA Testlerinin KLİNİK UYGULAMALARI

Maternal kandan alınan plazma örneğinde tüm hücre yapılarının uzaklaştırılması



DNA'nın ekstraksiyonu  
(Minör oranda fetal DNA(%10) + Major oranda maternal DNA (%90))

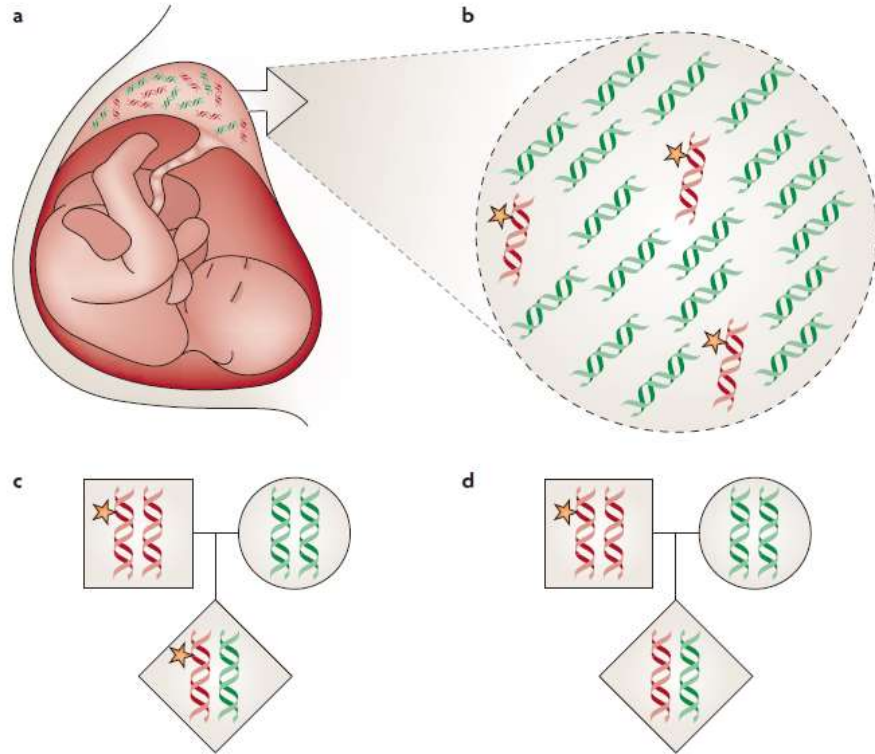
Kalitatif Yöntemler;  
Maternal ve fetal DNA  
polimorfizm/değişimlerini  
tanır

**TANI**

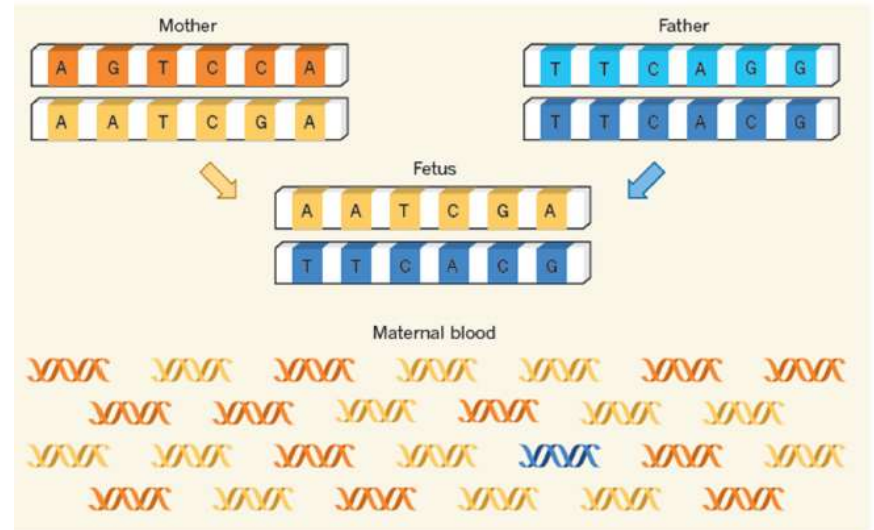
Kantitatif Yöntemler;  
Normal ile karşılaştırma esasına göre  
tanır

**TARAMA**

# Kalitatif yöntemle PATERNAL mutasyonun/özelliklerin fetusta TANISI



## Non-invasive prenatal diagnosis (NIPD)



Analysis by: Next Generation Sequencing (NGS)  
Massive Parallel Shotgun Sequencing (MPSS)



# Kantitatif Yöntem; Fetus NORMAL

Anne 46 kromozom + fetus 46 kromozom

Başlangıçtaki DNA Havuzu



Anne ye ait  
DNA fragmanları

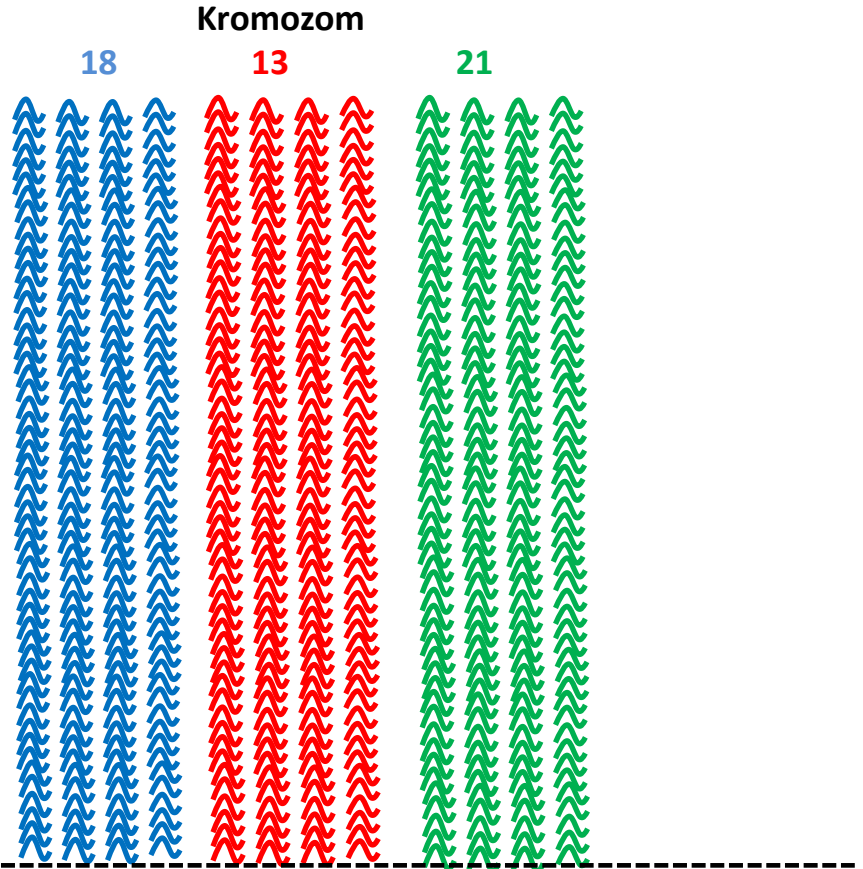
Yeni nesil  
dizileme ile  
amplifikasyon

1 : 1 : 1



Fetusa ait  
DNA fragmanları

Amplifikasyon sonrası DNA Havuzu



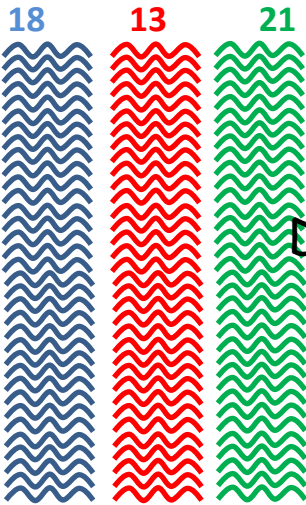
tüm AMPLİKONLARIN oranı eşit

# Kantitatif Yöntem; Fetus TRİZOMİK

Anne 46 kromozom + fetus 47 kromozom (47,+21)

Başlangıçtaki DNA Havuzu

Kromozom



Anne ye ait DNA fragmanları

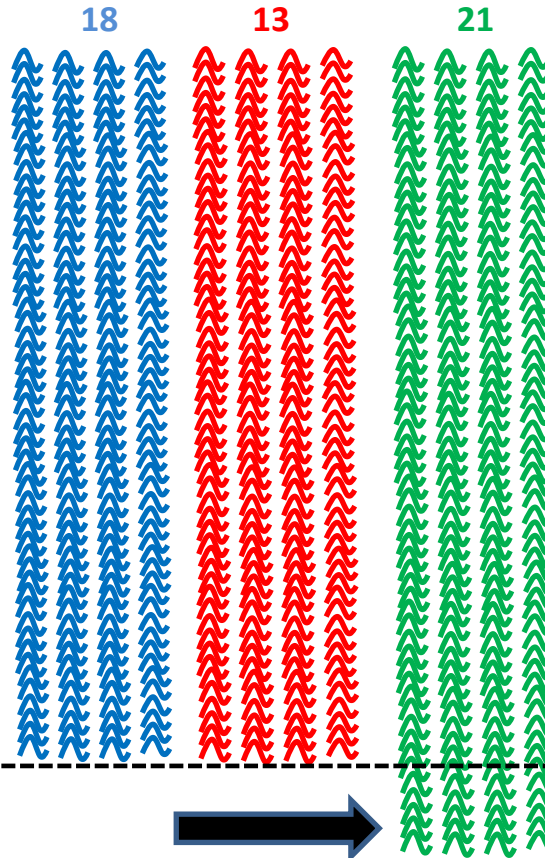
Yeni nesil dizileme ile amplifikasyon

Fetusa ait DNA fragmanları

1 : 1 : 1,1

Amplifikasyon sonrası DNA Havuzu

Kromozom



21. Kromozom AMPLİKONLARINDA artış

# Commercial landscape of noninvasive prenatal testing in the United States

Ashwin Agarwal, Lauren C. Sayres, Mildred K. Cho, Robert Cook-Deegan, and Subhashini Chandrasekharan

## Prenatal Diagnosis 2013, 33, 521-531

Table 1 Commercial landscape of noninvasive prenatal testing for fetal aneuploidy in the United States

	Sequenom	Verinata Health	Ariosa Diagnostics	Natera
Test name	MaterniT21 Plus <sup>13</sup>	Verifi <sup>15</sup>	Harmony Prenatal Test <sup>18</sup>	Panorama Prenatal Test <sup>24</sup>
Platform	SEQureDx technology incorporating massively parallel shotgun sequencing <sup>13</sup>	Massively parallel sequencing using SAFer algorithm <sup>15</sup>	DANSR technology incorporating targeted sequencing and FORTE algorithm <sup>79,80</sup>	Next-generation SNP-based Targeted Aneuploidy Testing <sup>24</sup>
Conditions	Trisomy 13, trisomy 18, trisomy 21, and sex chromosome aneuploidies <sup>13</sup>	Trisomy 13, trisomy 18, trisomy 21, sex chromosome aneuploidies, and fetal sex <sup>15</sup>	Trisomy 13, trisomy 18, and trisomy 21 <sup>18</sup>	Trisomy 13, trisomy 18, trisomy 21, and sex chromosome aneuploidies <sup>24,81,82</sup>
Cost	\$1700 out-of-pocket, \$235 co-pay with insurance coverage, and \$2900 directly billed to insurers <sup>83,84</sup>	\$295 out-of-pocket, \$200 co-pay with insurance coverage, and \$1200 directly billed to insurers <sup>16,97</sup>	\$795 out-of-pocket and \$95 co-pay with insurance coverage <sup>18-20,84</sup>	Unknown out-of-pocket and \$1495 directly billed to insurers <sup>24</sup>
Turnaround	8 to 10 days <sup>10</sup>	8 to 10 days <sup>15</sup>	8 to 10 days <sup>18</sup>	15 days <sup>24</sup>
Market entry	October 2011 <sup>83</sup>	March 2012 <sup>15</sup>	May 2012 <sup>6</sup>	December 2012 <sup>24</sup>
Marketing	Through physicians <sup>13</sup>	Through physicians <sup>15</sup>	Through physicians <sup>18</sup>	Through physicians <sup>24</sup>
Regulatory status	CAP accredited, CLIA certified, plans to submit an MD PMA application <sup>13,85,86</sup>	CAP accredited, CLIA certified, plans to submit an IVD PMA application <sup>15</sup>	CAP accredited, CLIA certified <sup>18</sup>	CAP accredited, CLIA certified <sup>82</sup>
Primary publications	Ehrich <i>et al.</i> <sup>87</sup> , Bombard <i>et al.</i> <sup>88</sup> , Palomaki <i>et al.</i> <sup>89</sup> , Palomaki <i>et al.</i> <sup>90</sup>	Sehnert <i>et al.</i> <sup>91</sup> , Bianchi <i>et al.</i> <sup>98</sup>	Sparks <i>et al.</i> <sup>79</sup> , Sparks <i>et al.</i> <sup>80</sup> , Ashoor <i>et al.</i> <sup>92</sup> , Norton <i>et al.</i> <sup>93</sup> , Ashoor <i>et al.</i> <sup>94</sup> , Nicolaides <i>et al.</i> <sup>95</sup>	Zimmermann <i>et al.</i> <sup>81</sup>

CLIA, Clinical Laboratory Improvement Amendments; CAP, College of American Pathologists; DANSR, Digital Analysis of Selected Regions; IVD, *In vitro* diagnostic product; PMA, Pre-market Approval; SNP, Single nucleotide polymorphism.



# Noninvasive prenatal testing for aneuploidy—ready for prime time?

Lyn S. Chitty, Melissa Hill, Helen White, David Wright, Stephen Morris,

*American Journal of Obstetrics & Gynecology*, APRIL 2012

Study	Method	Total no. samples tested	No. normal samples tested (true negatives)	No. aneuploid samples tested (true positive)	Sensitivity, % (95% CI) <sup>a</sup>	Specificity, % (95% CI) <sup>a</sup>
Lo et al <sup>16</sup>	RNA allelic ratio	67	57 (55)	10 (9)	90 (60.6–99.5)	96.5 (89.4–99.4)
Tsui et al <sup>17</sup>	RNA allelic ratio	62	58 (51)	4 (4)	100 (47.3–100)	89.7 (80.6–95.4)
Fan et al <sup>18,19</sup>	MPS	18	T21 cohort: 9 (9) T18 cohort: 16 (16) T13 cohort: 17 (17)	T21: 9 (9) T18: 2 (2) T13: 1 (1)	T21: 100 (71.8–100) T18: 100 (22.4–100) T13: 100 (5–100)	T21: 100 (71.8–100) T18: 100 (82.9–100) T13: 100 (83.8–100)
Chiu et al <sup>20</sup>	MPS	28	14 (14)	14 (14)	100 (80.7–100)	100 (80.7–100)
Ghanta et al <sup>21</sup>	Tandem SNP	27	20 (20)	7 (7)	100 (65.2–100)	100 (86.1–100)
Tong et al <sup>22</sup>	Differential methylation	29	24 (23)	5 (5)	100 (55–100)	95.8 (81.7–99.8)
Papageorgiou et al <sup>23</sup>	Differential methylation	40	26 (26)	14 (14)	100 (80.7–100)	100 (89.2–100)
Deng et al <sup>24</sup>	RT-MLPA	113	87 (87)	25 (23)	92 (77–98.6)	100 (96.6–100)
Chiu et al <sup>25</sup>	MPS	15	10 (10)	5 (5)	100 (54.9–100)	100 (74.2–100)
Sehnert et al <sup>26</sup>	MPS	47	T21 cohort: 34 (34) T18 cohort: 39 (39) T13 cohort: 46 (46)	T21: 13 (13) T18: 8 (8) T13: 1 (no call)	T21: 100 (79.5–100) T18: 100 (68.8–100) T13: –	T21: 100 (91.6–100) T18: 100 (92.6–100) T13: 100 (93.7–100)
Chen et al <sup>27</sup>	MPS (2 plex)	289	T13 cohort: 264 (261) T18 cohort: 252 (248)	T18: 37 (34) T13: 25 (25)	T18: 91.9 (80.4–97.8) T13: 100 (88.8–100)	T18: 98.9 (97.1–99.7) T13: 98.4 (96.4–99.4)
Ehrich et al <sup>28</sup>	MPS (4 plex)	449	410 (409)	39 (39)	100 (92–100)	99.7 (98.8–99.9)
Lau et al <sup>29</sup>	MPS (12 plex)	108	T21 cohort: 97 (97) T18 cohort: 98 (98) T13 cohort: 106 (106)	T21: 11 (11) T18: 10 (10) T13: 2 (2)	T21: 100 (76.2–100) T18: 100 (74.5–100) T13: 100 (22.4–100)	T21: 100 (97–100) T18: 100 (97–100) T13: 100 (97.2–100)
Chiu et al <sup>9</sup>	MPS (8 plex)	657	571 (6)	86 (68)	79.1 (70.6–86)	98.9 (97.9–99.5)
Chiu et al <sup>9</sup>	MPS (2 plex)	232	146 (3)	86 (86)	100 (96.6–100)	97.9 (94.8–99.8)
Palomaki et al <sup>9</sup>	MPS	1683	1471 (1468)	212 (209)	98.6 (96.4–99.6)	99.8 (99.5–99.9)
Sparks et al <sup>14</sup>	Targeted MPS	167	123 (123)	T21: 36 (36) T18: 8 (8)	T21: 100 (92.1–100) T18: 100 (68.8–100)	T21: 100 (97.6–100) T18: 100 (97.6–100)
Ashoor et al <sup>15</sup>	Targeted MPS	397	297 (297)	T21: 50 (50) T18: 50 (49)	T21: 100 (94.2–100) T18: 98 (90.1–99.9)	T21: 100 (99–100) T18: 100 (99–100)

CI, confidence interval; MLPA, multiplex ligation-dependent probe amplification; MPS, massively parallel sequencing; RT, reverse transcriptase; SNP, single nucleotide polymorphisms; T, trisomy.

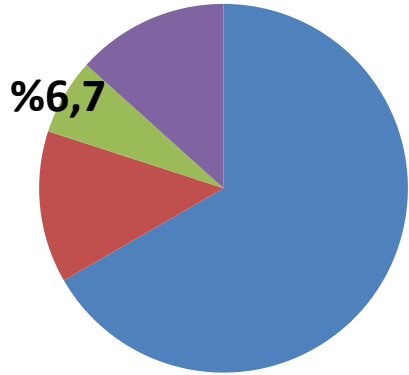
<sup>a</sup>All CIs have been calculated by one of the authors (H.W.) using data published in the articles quoted.

Chitty. Noninvasive prenatal testing for aneuploidy. *Am J Obstet Gynecol* 2012.

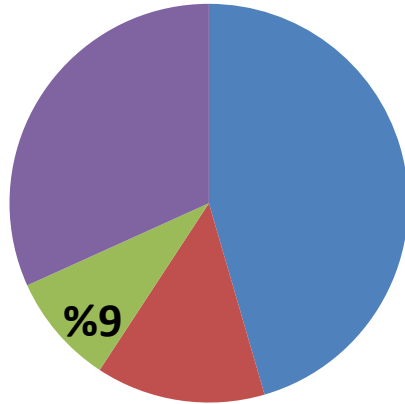
**CVS (n:2 453) ve AS (n:23 338) serilerinde saptanan anomaliler içinde sık görülen 5 anöploidinin oranı ve cf-DNA testinin (hassasiyeti %100 kabul edildiğinde) bu anomalileri hipotetik yakalama oranı ve rezidual riskler (PRETAM+PREMED, 1989-2011)**

İnvaziv yöntem, endikasyon, saptanan kromozom anomalileri, ve % leri	cf-DNA testi ile yakalanabilecek anomaliler		cf-DNA testi ile yakalanamayan anomaliler		Endikasyon gruplarındaki rezidual risk
	n	%	n	%	%
<b>CVS-ileri anne yaşı</b> 335'de 15 anomali <b>%4,5</b>	12	66,8	3	<b>33,2</b>	<b>%0,9      1:111</b>
<b>AS- ileri anne yaşı</b> 10 430'da 233 anomali <b>%2,2</b>	135	57,9	98	<b>42,1</b>	<b>%0,9      1:111</b>
<b>CVS- Tarama testi +</b> 282'de 53 anomali <b>%18,8</b>	39	73,6	14	<b>26,4</b>	<b>%5      1:20</b>
<b>AS- Tarama testi +</b> 6749'da 185 anomali <b>%2,7</b>	120	64,9	65	<b>35,1</b>	<b>%1      1:100</b>
<b>CVS- Patolojik USG</b> 824'de 244 anomali <b>%29,6</b>	199	81,6	45	<b>18,4</b>	<b>%5,5      1:18</b>
<b>AS- Patolojik USG</b> 4442'de 378 anomali <b>%8,5</b>	298	78,8	80	<b>21,2</b>	<b>%1,8      1:56</b>

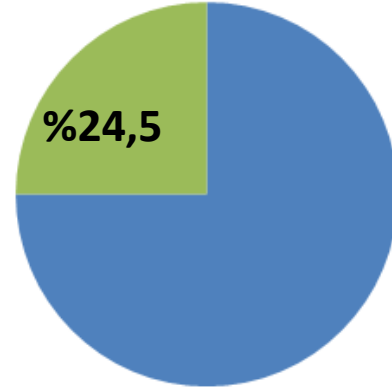
**CVS-İAY**



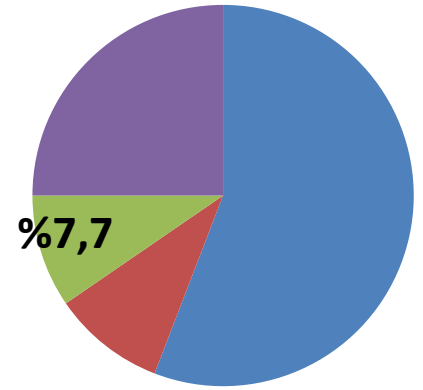
**AS-İAY**



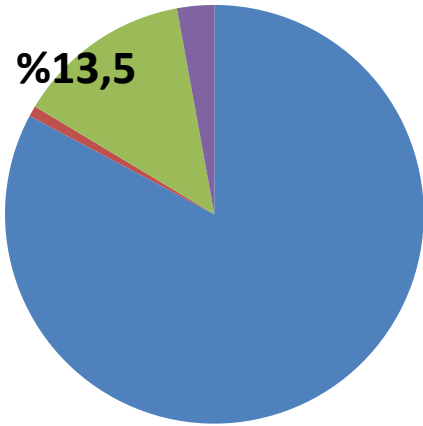
**CVS-ST**



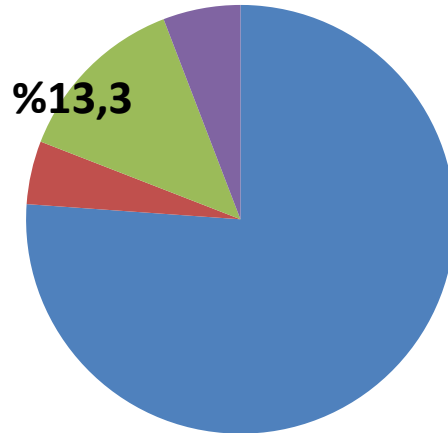
**AS-ST**







**CVS-PatUSG**



**AS-PatUSG**



-  cf DNA ile yakalanabilecek majör anomaliler
-  cf DNA ile yakalanabilecek minör anomaliler
-  cf DNA ile yakalanamayacak majör anomaliler
-  cf DNA ile yakalanamayacak minör anomaliler



# Comparison of NIPT Technology Claims

Sensitivity False Positive Rate	Sequenom MaterniT21 plus	Verinata Verifi	Ariosa Harmony	Natera Panorama™
Methodology	MPSS	MPSS with SAFeR	Targeted Sequencing with FORTE	Targeted Sequencing with SNPs
Trisomy 21 (Down Syndrome)	>99.9% 0.2%	>99.9% 0.2%	>99% <0.1%	>99% 0%
Trisomy 18 (Edwards Syndrome)	>99.9% 0.3%	97.4% 0.4%	>98% <0.1%	>99% 0%
Trisomy 13 (Patau Syndrome)	91.7% 0.9%	87.5% 0.1%	80% <0.1%	>99% 0%
45,X (Monosomy X)	Not evaluated	95.0% 1.0%	Not evaluated	>99% 0%

(1) Zimmermann et al. Prenat Diag 2012 (2) Natera Internal Data (3) Rabinowitz et al. Presented at ASHG 2012

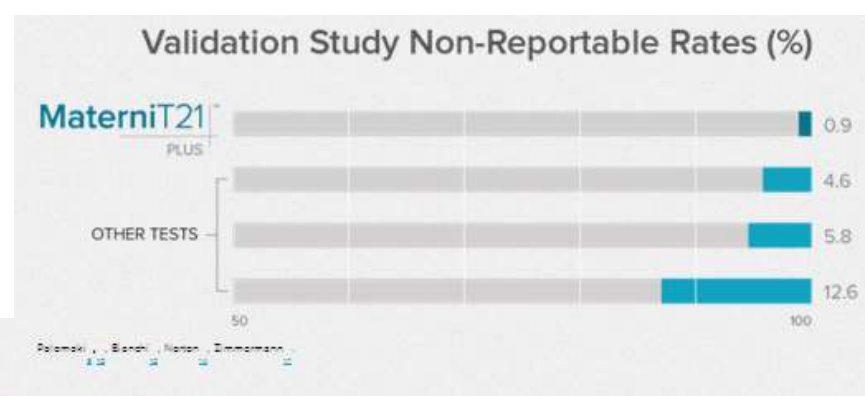
(2) Downloaded on February 5, 2013

<http://www.sequenomcmm.com/Home/Health-Care-Professionals/Trisomy-21/Performance-Data>

(3) Downloaded on February 5, 2013 <http://www.verinata.com/providers/provider-overview/>

(4) Downloaded on February 5, 2013 <http://www.ariosadx.com>

# Sequenom - LifeCodexx - MaterniT21 plus



## MaterniT21 PLUS Test Validation

CLINICAL VALIDATION STUDY	POSITIVE RESULTS	SENSITIVITY	SPECIFICITY
<b>1,696 SAMPLES</b> DNA Sequencing of Maternal Plasma to Detect Down syndrome: An International Clinical Validation Study <small>Genet Med. 2011;13(11):913-920.</small>	<b>210 OF 212 Trisomy 21</b>	<b>99.1%</b>	<b>99.9%</b>
<b>1,988 SAMPLES</b> DNA Sequencing of Maternal Plasma Reliably Identifies Trisomy 18 and Trisomy 13, as well as Down syndrome: An International Collaborative Study <small>Genet Med. 2012;14(3):296-305.</small>	<b>59 OF 59 Trisomy 18</b>	<b>&gt;99.9%</b>	<b>99.6%</b>
	<b>11 OF 12 Trisomy 13</b>	<b>91.7%</b>	<b>99.7%</b>
<b>2,015 SAMPLES</b> DNA Sequencing of Maternal Plasma to Identify Down syndrome and Other Trisomies in Multiple Gestations <small>Prenat Diagn. 2012;32(8):730-734.</small>	<b>8 OF 8</b> 7 of Trisomy 21 1 of Trisomy 13	<b>DETECTION RATE: &gt;99.9%</b>	
<b>Y CHROMOSOME</b>			
<b>2,107 SAMPLES</b> Accuracy of noninvasive prenatal fetal sex determination <small>Poster presented at American Society of Human Genetics Meeting (ASHG); 2012; San Francisco.</small>	<b>ACCURACY: 99.4%</b>		
COMBINED SEX ANEUPLOIDIES	POSITIVE RESULTS	SENSITIVITY	SPECIFICITY
<b>420 SAMPLES</b> Noninvasive prenatal detection of sex chromosomal aneuploidies by sequencing circulating cell-free DNA from maternal plasma. <small>Prenat Diagn. 2013;33(6):591-597.</small>	<b>25 OF 26</b>	<b>96.2%</b>	<b>99.7%</b>

**Trizomiler; 21, 18, 13, X and Y ve 16 ve 22**  
**Mikrodeletions;**  
 del 22q11.2 (DiGeorge s.),  
 5p- (Cri-du-chat s.),  
 del 15q11.2 (Prader-Willi/Angelman s.),  
 del 1p36

# Verinata - Verifi

## Test Performance<sup>1</sup>

As sequencing technology rapidly evolves, our research team has analyzed and implemented several changes to the testing procedure that yield enhanced test performance.

	N	Sensitivity	95% CI	Specificity	95% CI
21	500	>99.9% (90/90)	96-100.0	99.8% (409/410)	98.7-100.0
18	501	97.4% (37/38)	86.2-99.9	99.6% (461/463)	98.5-100.0
13	501	87.5% (14/16)	61.7-98.5	>99.9% (485/485)	99.2-100.0
Both 'Aneuploidy Detected' and 'Aneuploidy Suspected (Borderline Value)' results were included for performance calculation.					
MX	508	95.0% (19/20)	75.1-99.9	99.0% (483/488)	97.6-99.7

The verifi<sup>®</sup> test now includes an option for the most common sex aneuploidies, providing information previously known only through invasive results.

	N	Sensitivity	95% CI	Specificity	95% CI	Accuracy	95% CI
XX	508	97.6% (243/249)	94.8-99.1	99.2% (257/259)	97.2-99.9	98.4%	96.9-99.3
XY	508	99.1% (227/229)	96.9-99.9	98.9% (276/279)	96.9-99.8	99.0%	97.7-99.7
XXX, XXY, XYY	Limited data of these more rare aneuploidies preclude performance calculations.						

Watch Now!

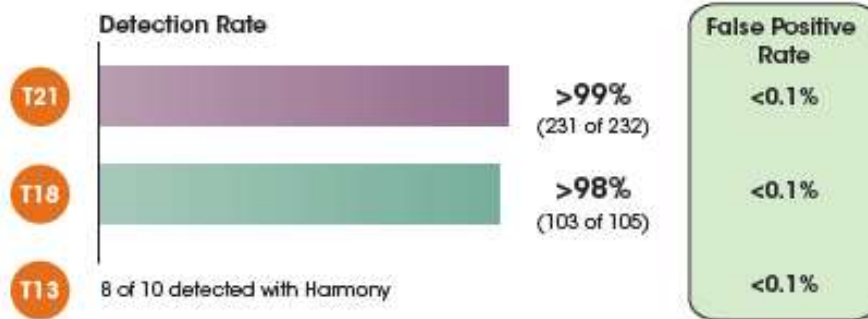
"NIDT in Clinical Practice Today"



Presented by  
Diana Bianchi, MD

# ARIOSIA - Harmony test

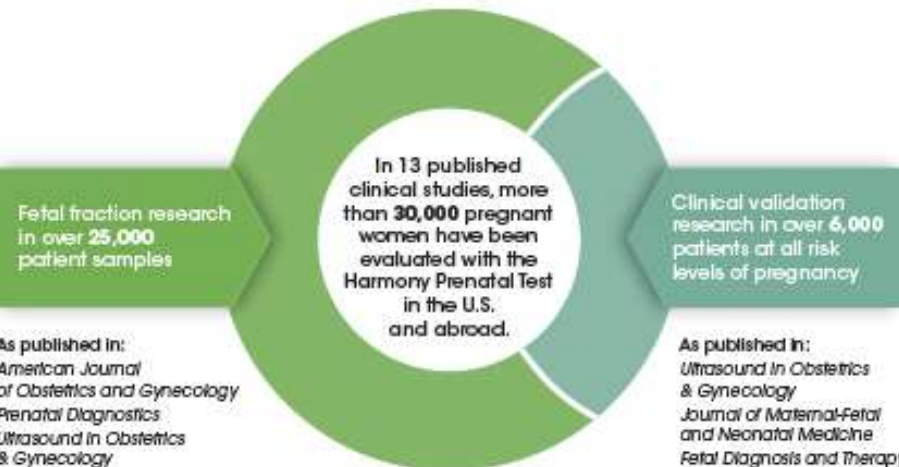
Studied in over 6,000 patients, including >2,000 average-risk women.



Detection and false positive rates calculated based on risk cut-off of 1/100 (1%)<sup>4</sup>

- Extremely low cumulative false positive rate
- Optional X,Y sex chromosome analysis with 99% accuracy for fetal sex (95% CI: 95-100)<sup>8</sup>

Exceptional clinical validation, laboratory performance, and ongoing research<sup>1-6, 9,12</sup>





# Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18

Ghalia Ashoor, MD; Argyro Syngelaki, RM; Marion Wagner, MD; Cahit Birdir, MD; Kypros H. Nicolaides, MD

**OBJECTIVE:** The purpose of this study was to assess the prenatal detection rate of trisomy 21 and 18 and the false-positive rate by chromosome-selective sequencing of maternal plasma cell-free DNA.

**STUDY DESIGN:** Nested case-control study of cell-free DNA was examined in plasma that was obtained at 11-13 weeks before chorionic villosus sampling from 300 euploid pregnancies, 50 pregnancies with trisomy 21, and 50 pregnancies with trisomy 18. Laboratory personnel were blinded to fetal karyotype.

**RESULTS:** Risk scores for trisomy 21 and 18 were given for 397 of the 400 samples that were analyzed. In all 50 cases of trisomy 21, the risk score for trisomy 21 was  $\geq 99\%$ , and the risk score for trisomy 18 was  $\leq 0.01\%$ . In all 50 cases of trisomy 18, the risk score for trisomy 21 was  $\leq 0.01\%$ , and the risk score for trisomy 18 was  $\geq 99\%$  in 47

cases, 98.8% in 1 case, 88.5% in 1 case, and 0.11% in 1 case. In 3 of the 300 euploid pregnancies (1%), no risk score was provided, because there was failed amplification and sequencing. In the remaining 297 cases, the risk score for trisomy 21 was  $\leq 0.01\%$ , and the risk score for trisomy 18 was  $\leq 0.01\%$  in 295 cases, 0.04% in 1 case, and 0.23% in 1 case. Therefore, the sensitivity for detecting trisomy 21 was 100% (50/50 cases); the sensitivity for trisomy 18 was 98% (49/50 cases), and the specificity was 100% (297/297 cases).

**CONCLUSION:** In this study, chromosome-selective sequencing of cell-free DNA separated all cases of trisomy 21 and 98% of trisomy 18 from euploid pregnancies.

**Key words:** first trimester, trisomy 18, trisomy 21

HARMONY

400 kan örneği

300 öploid 3 örnekte risk skoru belirlenememiş.

297 örnekte risk değeri  $\leq 0,01\%$  specificity %100

50 T21

50/50 risk değeri  $\geq 99\%$  sensitivity %100

50 T18

47/50 risk değeri  $\geq 99\%$

1/50 risk değeri  $\geq 98,8\%$

1/50 risk değeri  $\geq 88,5\%$

1/50 risk değeri 0,11%

Toplam 49/50 sensitivity %98

FNR %2

# Trisomy 13 detection in the first trimester of pregnancy using a chromosome-selective cell-free DNA analysis method

G. ASHOOR\*, A. SYNGELAKI\*, E. WANG†, C. STRUBLE†, A. OLIPHANT†, K. SONG† and K. H. NICOLAIDES\*‡

\*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; †Ariosa Diagnostics, Inc., San Jose, CA, USA; ‡Department of Fetal Medicine, University College London Hospital, London, UK

2002 örnekten 53 ünde sonuç alınamamış, 1949 örnekte risk skoru alınmış.

10 T13	risk skoru	> 99%	8/10	sensitivity	80.0%
				FNR	20%
1939 öploid	risk skoru	< 0.01%	1937/1939	specificity	99.9%
		0.79%	1/1939		
		> 99%	1/1939	FPR	0.05% (95% CI, 0.0–0.3%)



## 30<sup>th</sup> Anniversary Issue of Prenatal Diagnosis

### HORIZON SCANNING

# Noninvasive prenatal diagnosis in 2020

Y. M. Dennis Lo<sup>1,2\*</sup>

<sup>1</sup>Centre for Research into Circulating Fetal Nucleic Acids, Li Ka Shing Institute of Health Science Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China

<sup>2</sup>Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China

NIPD IN 2020

make even such an application practically feasible. Furthermore, the rapid development in targeted sequencing, in which only selected parts of the genome are analyzed (Mamanova *et al.*, 2010), would further reduce the costs of this approach. Thus, I would predict that

by 2020, many groups would routinely be using massively parallel sequencing technology for the NIPD of multiple monogenic diseases from maternal plasma. Furthermore, as discussed above, the same tests would also provide diagnostic information on fetal chromosomal aneuploidies. Indeed, I would predict that by 2020, the sequencing of the complete fetal genome from maternal plasma would already have been achieved by a number of groups. These developments would likely lead to a drastic reduction in the use of invasive techniques, such as amniocentesis and chorionic villus sampling, at least in the more developed regions of the world. I would foresee that in 2020, there would be multiple articles in *Prenatal Diagnosis* debating about the ethical and social implications of the information explosion from NIPD.

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# Analysis of Cell-Free DNA in Maternal Blood in Screening for Aneuploidies: Meta-Analysis

M.M. Gil<sup>a</sup> R. Akolekar<sup>a,b</sup> M.S. Quezada<sup>a</sup> B. Bregant<sup>a</sup> K.H. Nicolaides<sup>a</sup>

<sup>a</sup>Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, and <sup>b</sup>Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK

## Abstract

**Objective:** To review clinical validation or implementation studies of maternal blood cell-free (cf) DNA analysis in screening for aneuploidies and to explore the potential use of this method in clinical practice. **Methods:** Searches of PubMed and MEDLINE were performed to identify all peer-reviewed articles on cfDNA testing in screening for aneuploidies between 2011, when the first such study was published, and 20 December 2013. **Results:** Weighted pooled detection rates (DR) and false-positive rates (FPR) in singleton pregnancies were 99.0% (95% CI 98.2–99.6) and 0.08% (95% CI 0.03–0.14), respectively, for trisomy 21; 96.8% (95% CI 94.5–98.4) and 0.15% (95% CI 0.08–0.25) for trisomy 18; 92.1% (95% CI 85.9–96.7) and 0.20% (95% CI 0.04–0.46) for trisomy 13; 88.6% (95% CI 83.0–93.1) and 0.12% (95% CI 0.05–0.24) for monosomy X, and 93.8% (95% CI 85.9–98.7) and 0.12% (95% CI 0.02–0.28) for sex chromosome aneuploidies other than monosomy X. For twin pregnancies, the DR was 94.4% (95% CI 74.2–99.0) and the FPR was 0% (95% CI 0.00–1.84) for trisomy 21. **Conclusion:** An analysis of cfDNA in maternal blood provides effective screening for trisomies.

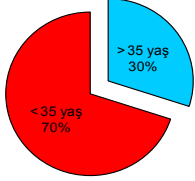
# Konjenital Malformasyonlar

Tanı → USG

- Yeni doğan sıklığı %2-4
- Etiyolojik faktörler;
  - Kromozom anomalileri
  - Tek gen hastalıkları
  - Multifaktöriyel hastalıklar
  - Maternal faktörler
  - Deformasyonlar

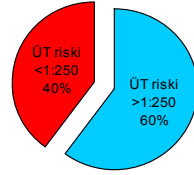
# TARAMA Testleri

İAY ile DS Yakalama Oranı



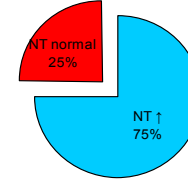
İleri anne yaşı

ÜT ile DS Yakalama Oranı



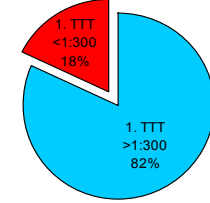
Üçlü test/  
Dörtlü test

NT ile DS Yakalama Oranı

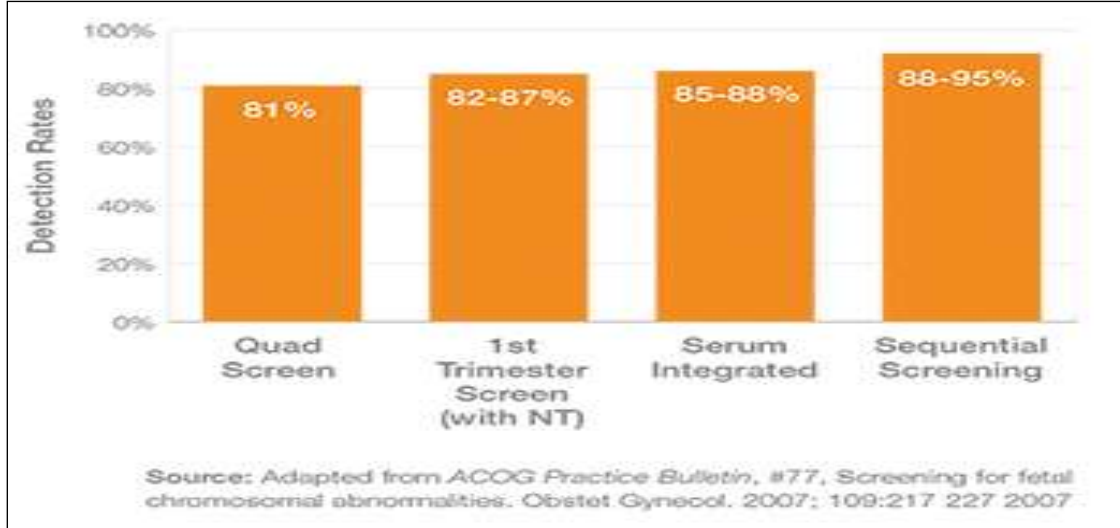


USG; NT ve  
diğer markerler

1. TTT ile DS Yakalama Oranı



11-14 hafta tarama



**MS- cell free DNA/RNA analizleri ile anöploidi taraması**

1989-2014/8 ay İTF-TGABD+PREMED

nonmozaik CVS - normal/moz AS karyotip (5/3090 - %0,16, 1:625)

	Endikasyon	CVS-DP	CVS-HK	Fetal doku	Sonuç	Gebelik akıbeti
1	1.TRİ	47,+13	47,+13	AS 46 I-FISH mos	GM - AS YN	USG N tahliye
2	PatUSG+1.TRİ	47,+16	47,+16	AS 46 I-FISH mos	GM - AS YN	tahliye
3	1.TRİ	47,+16	47,+16	AS 46	GM - AS YN	USG; IUGG+oligohidr.+ HI tahliye
4	1.TRİ+İAY	I-FISH +16	47,+16	AS 46	GM / CPM YP/UPD	USG N gebelik devam
5	PatUSG	yok	47,+16	AS 46 I-FISH N	CPM YP/UPD/GM?	Diafragma hernisi nedeniyle tahliye

**Konfirmasyon için AS'da I-FISH sonuçları ÇOK ÖNEMLİ !!!**



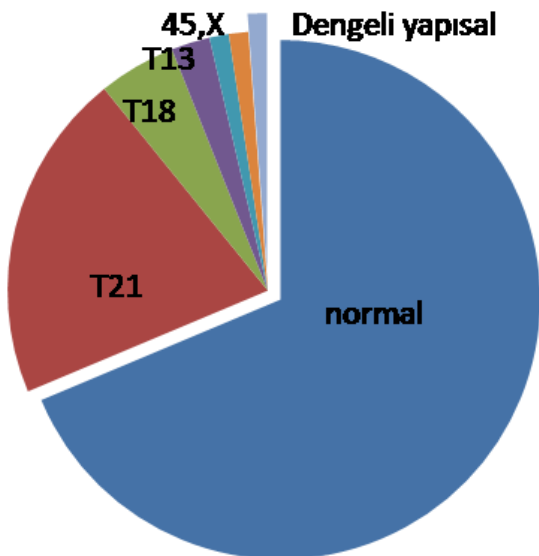
# CVS Serisi 2010-2014/8

## izole NT-CVS

toplam 83	n	%
normal	57	68,7
<b>T21</b>	17	<b>20,5</b>
<b>T18</b>	4	<b>4,8</b>
<b>T13</b>	2	<b>2,4</b>
<b>45,X</b>	1	<b>1,2</b>
47,XXX	1	1,2
dengeli yapısal	<b>1</b>	<b>1,2</b>

28,9%  
31,3%

47,XXX

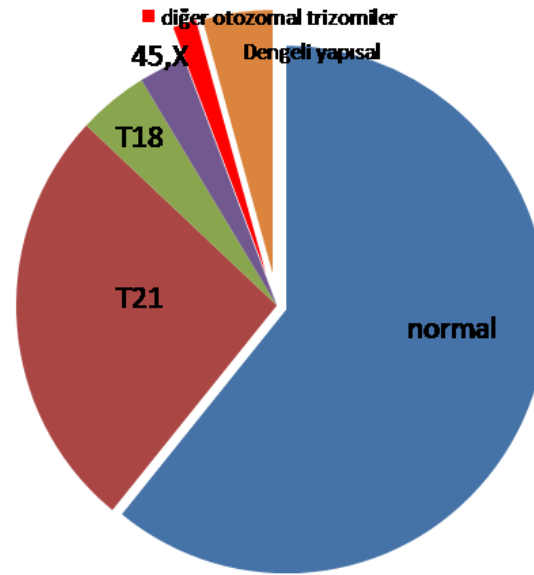


## NT+1.TTT-CVS

toplam 69	n	%
normal	42	60,1
<b>T21</b>	18	<b>26,1</b>
<b>T18</b>	3	<b>4,3</b>
<b>45,X</b>	2	<b>2,9</b>
diğer otozomal trizomiler	1	1,5
dengeli yapısal	3	4,3

33,3%  
39,1%  
5,8%

diğer otozomal trizomiler  
45,X  
Dengeli yapısal





# CVS Serisi 2010-2014/8

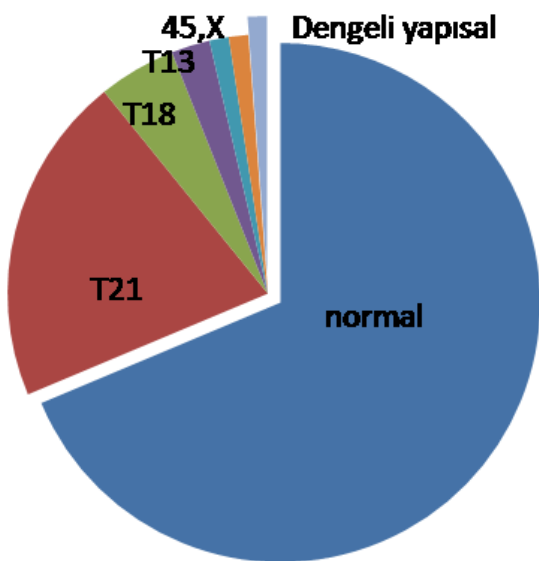
## izole NT-CVS

toplam 83	n	%
normal	57	68,7
T21	17	20,5
T18	4	4,8
T13	2	2,4
45,X	1	1,2
47,XXX	1	1,2
dengeli yapısal	1	1,2

28,9%

31,3%

47,XXX



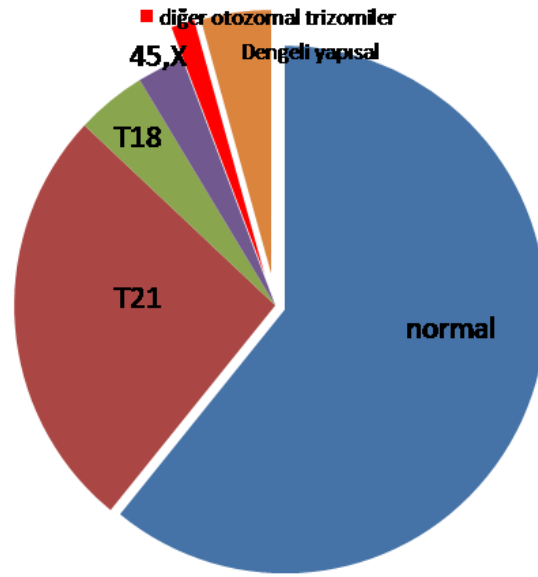
## NT+1.TTT-CVS

toplam 69	n	%
normal	42	60,1
T21	18	26,1
T18	3	4,3
45,X	2	2,9
diğer otozomal trizomiler	1	1,5
dengeli yapısal	3	4,3

33,3%

39,1%

5,8%



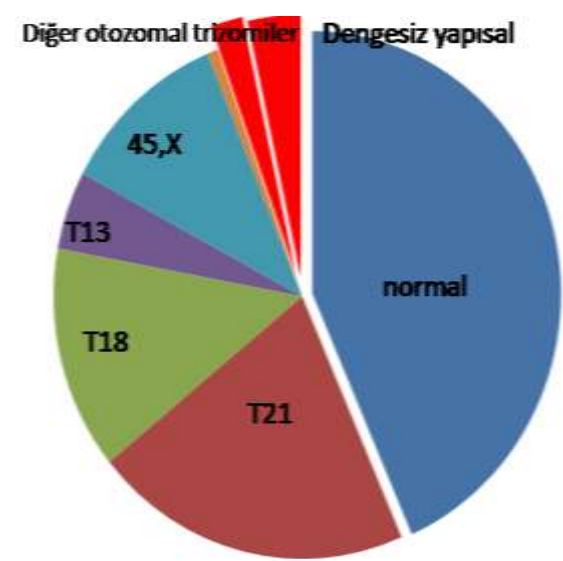
## NT+multiple anomaliler-CVS

toplam 145	n	%
normal	63	43,4
T21	30	20,7
T18	20	13,8
T13	7	4,8
45,X	16	11
47,XY	1	0,7
diğer otozomal trizomiler	3	2,1
dengesiz yapısal	5	3,5

51%

56,6%

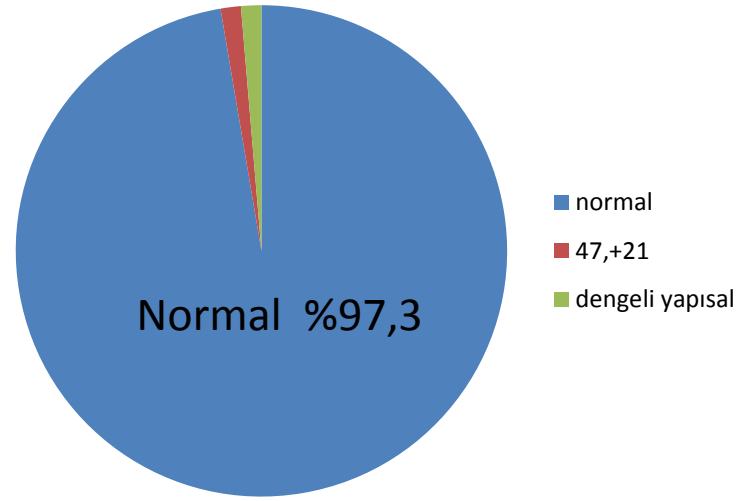
5,6%



# AS Serisi 2010-2014/8

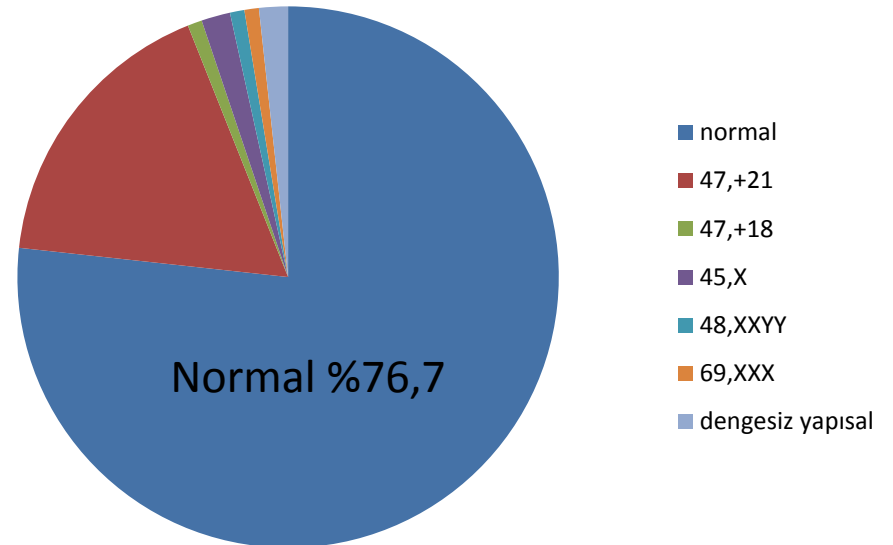
## İzole Ense Plisi artışı-AS

	n	%
toplam 75		
<b>abnormal</b>	<b>2</b>	<b>2,7</b>
normal	73	97,3
<b>47,+21</b>	<b>1</b>	<b>1,3</b>
dengeli yapısal	<b>1</b>	<b>1,3</b>

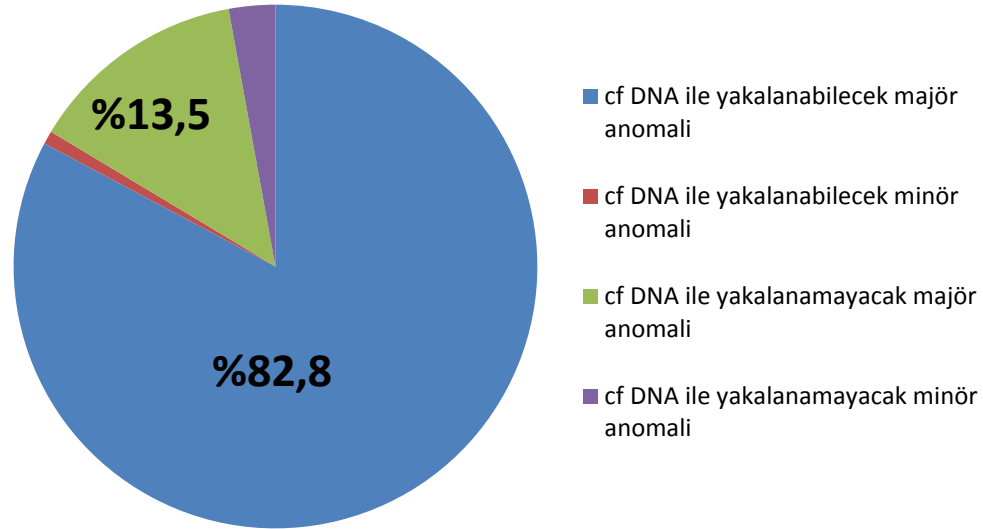


## EP+ multiple anomaliler-AS

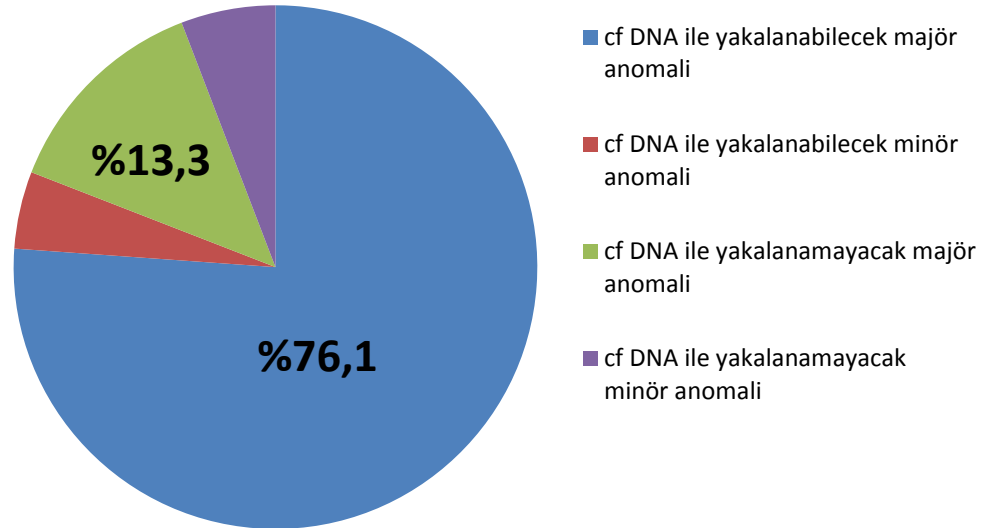
toplam 116	n	%
<b>abnormal</b>	<b>27</b>	<b>23,3</b>
normal	89	76,7
<b>47,+21</b>	<b>20</b>	<b>17,2</b>
<b>47,+18</b>	<b>1</b>	<b>0,9</b>
<b>45,X</b>	<b>2</b>	<b>1,7</b>
48,XXYY	1	0,9
69,XXX	<b>1</b>	<b>0,9</b>
dengesiz yapısal	<b>2</b>	<b>1,7</b>



## CVS-PatUSG



## AS-PatUSG



## 1989-2014/8 ay İTF-TGABD+PREMED

## Mozaik CVS (n:25, %0,8)

	Endikasyon	CVS-DP	CVS-HK	Fetal doku	Sonuç	Gebelik akıbeti
1	PatUSG	46	47,+21	yok	DP YN	IUMF
2	PatUSG	46	47,+21	AS IFISH T21	DP YN	tahliye
3	PatUSG+1.TRİ	46	47,+18	yok	DP YN	tahliye
4	1.TRİ	46 IFISH N	47,+18	AS IFISH T18	DP YN	tahliye
5	PatUSG	92	47,+13/92	AS 47,+13	DP YN	tahliye
6	PatUSG	46	47,+7	yok	DP YN	tahliye
7	PatUSG	46	46/47,+8	yok	DP YN	tahliye
8	İAY+KAÇ	46	46/47,+9	yok	DP YN	tahliye
9	PatUSG	46	46/47,+9	AS 46	DP YN	tahliye
10	KAE+PatUSG	46,t(11q;22q) IFISH mos	46,t(11q;22q)/47,t(11q;22q)+9	yok	DP YN	tahliye
11	PatUSG	46	46/47,+10	yok	DP YN	tahliye
12	ÜT	46	46/47,+15	AS 46	DP YN	tahliye
13	1.TRİ	46 IFISH mos	47,+16	AS IFISH mos	DP YN	tahliye
14	ÜT+İAY	46	46/47,+16	yok	DP YN	IUMF
15	PatUSG	46	69,XXX	yok	DP YN	tahliye
16	PatUSG	46	69,XXX	yok	DP YN	tahliye
17	PatUSG	46	46/46,dup(11)(p11.2p15.5)dn	46,dup(11)(p11.2p15.5)	DP YN	tahliye
18	PatUSG+1.TRİ	46	45,der(15;18)(p10;p10)dn	45,der(15;18)(p10;p10)	DP YN	tahliye
19	PatUSG+İAY	46,5p+	46,del(5)(p13.3->pter)dn	46,del(5)(p13.3->pter)	DP YN	tahliye
20	1.TRİ	47,+16	üreme yok	AS 46/47+16	GM	tahliye
21	PatUSG+İAY	46/47,+18	47,+18	yok	GM	tahliye
22	PatUSG+1.TRİ	4n	2n/4n	yok	GM	tahliye
23	PatUSG	2n/4n	2n/4n	yok	GM	tahliye
24	PatUSG+1.TRİ	46/47,+idic(14/22)	46/47,+idic(14/22)	yok	GM	doğdu
25	PatUSG+İAY	47,+22	46	yok	HK YN?	tahliye

CPM tiplerinin sıklıkları EUCROMIC 1986-1992  
48 laboratuvar n:62 865 CVS  
Hahnemann JM&Vejerslev LO, 1997, Prenat Diagn:17;801

normal	59 592	% 94.8	
nonmozaik anormal	2 321	% 3.7	
<b>şüpheli sonuç</b>	<b>952</b>	<b>% 1.51</b>	
gerçek mozaik	77	% 0.12	} cf ??
nonmoz. CV/moz. Fetus	12	% 0.02	
yanlış pozitif CPM	656	% 1.04	} cf ->CVS/AS
nonmozaik CPM	96	% 0.15 !!	
<b>yanlış negatif CPM</b>	<b>19</b>	<b>% 0.03!!</b>	<b>cf Normal</b>
sınıflandırılmayan	92	% 0.15	

## Ayrıca Türkiye özelinde;

1. Bugüne kadarki uygulamalar nasıl yürütüldü?
2. Genetik "danışma" veriliyor mu?
3. Sonuçlar nasıl ve bunlar kayıt altında mı?
4. Ekstra bir ücret ile yapılan bu tıbbi testte "sorumluluk" kimde?
5. Cinsiyet tanısının kötüye kullanımı nasıl kontrol edilecek?
6. Genetik materyalin topluca yurtdışına gönderilmesi için Sağlık Bakanlığının izni gerek
7. cf-DNA testinin yeri nerededir?