Maternal kanda serbest fetal DNA

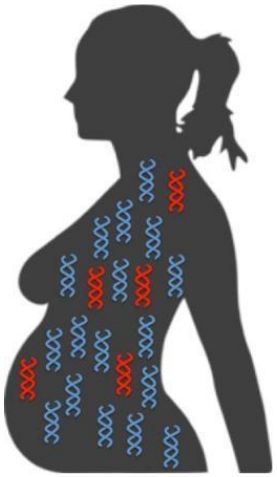
Prof. Dr. Recep Has
İstanbul Tıp Fakültesi
Kadın Doğum/Perinatoloji

Serum/plazmada serbest DNA-RNA

- 1948-Mandel P, Metais P
  - Serumda nükleik asit
- 1951- Ayala W
  - Romatoid artrit
- 1966- Tan EM
  - SLE
- 1977- Leon SA
  - Kanser
- 1989- Stroun M
  - Kanser
- Kanser
  - Myeloid, epiteloid, solid
    - Tanı
    - Prognoz
- Travma
  - Hasar derecesi
- İnme
  - Hasar derecesi

Maternal Kanda fetal DNA

- Tek kopya fetal DNA
  - Lo YM, Lancet, 1990
- Rh geni
  - Lo YM, Lancet, 1993
- Cinsiyet tayini (Y krom)
  - Lo YM, Hum Genet, 1993



  - High Sequencing Systems, Illumina

- Quantitative real-time PCR
- Digital PCR

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 Wainscoat

- Lo YMD, Lancet, 1997
  - 12-40 hf arası
    - 30 erkek fetus
    - 13 kız fetus kontrol

GH	Cff-DNA	Fetal hücre	Kat
11-17 hf	%3,4	%0,001	**3400**
37-43 hf	%6,2	%0,01	**620**

Lo YM; 1998, Am J Hum Genet

Maternal kanda fetal DNA

- Trafik iki yönlü
  - fetal kanda maternal DNA (%0,9)
  - maternal kanda fetal DNA (%14,3) *(Sekizawa, 2003)*
- İdrarda da bulunur *(Tsoi NBY 2012)*
- Fetal DNA plasenta (trofoblast) kökenli
  - 4-5. haftadan itibaren *(Guibert, 2003)*
  - Plasental karyotipi yansıtır *(Masuzaki, 2004)*
  - Anembryonik gebeliklerde saptanabilir *(Alberry, 2007)*

- Konsantrasyon GH ile artar
- Klirensi hızlıdır (30 dk) *(Lo, 1998)*
  - Doğumdan sonra tamamen kaybolur *(Lo, 1999)*

- 11-14 hafta
- Ortalama cff-DNA %10
- %4'ün altında analizi zor
  - Obezite ile azalıyor
  - CRL, PAPP-A, sHCG, sigara ile artıyor

Prenatal tanıda serbest fetal DNA

- Annede (-), fetusta (+) (babadan veya de Novo) genlerin tanısı
  - Rh negatif anne - Rh pozitif fetus
    - 2007'den itibaren
  - Fetal cinsiyet tayini *(SRY)*
    - X'e bağlı hast. (Kız ise işlem gereksiz)
    - Ambigius genitalia
    - KAH > steroide başlamak için (fetus erkekse gereksiz)
  - Tek genetik hastalıkları
    - Baba hasta - otozomal dominant hastalıklar
      - Akondroplazi, Huntington
    - Ebeveynlerin farklı mutasyonlar taşıdığı resesif hastalıklar
      - Kistik fibrozis

Aneuploidi- serbest fetal DNA

- Serbest RNA
  - PLAC4 gen sekansları
  - Farklı alellerin oranlarının ölçümü (SNP's)
- **Serbest DNA**
  - **Massively parallel (next-generation) sequencing: MPS**
  - **Digitally Analysis of Selected Regions: DANSR**
  - **Targeted sequencing of SNP's**

Full otomatik

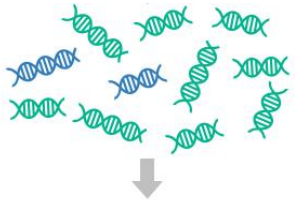
Firmalar/Yöntemler

- ABD
- Clinical Laboratory Improvement Amendments (CLIA) sertifikalı
  - Sequenom- BİOGEN (MateriniT21-T21 plus)
  - Verinata- (Prenatal Test)
  - Aria Diagnostics- GELAB (Harmony)
  - Natera- BURÇ (Panorama)

- Çin
  - BGI-GENOKS (Nifty)

-MPSS
-DANSR
-SNP

MPS



Full genom

TCCGCCCAGGCCATGAGGGACCTGGAAATGGCTGAT chr21
GGCCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
GACACGGTGGAGCTCGGCCACACCAGGCCCAGCTGG chr14

Fetal cfDNA

Maternal cfDNA

T21 de %10 daha fazla 21 Krom cfDNA

Z skoru

VS

Kromozom: 1 2 3 ..... 21 **Trizomi 21**

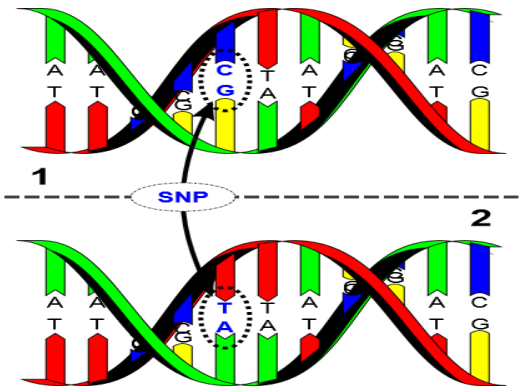
DANSR

- Hedef kromozomun bir bölgesi
- Lokus-spesifik oligonukleotid kullanılır

- Sadece ilgilenilen bölgeyi okur
  - Daha ucuz
  - Daha hızlı
  - Olasılık rakamı verir

Targeted Sequencing of SNP's
(Single Nükleoid Polimorfizmi)

- DNA dizisinde tek bir nukleotid (A,T,C veya G) diziliminde değişiklik
  - Kişiler arasında
  - Kromozomlar arasında



- Araştırılan kromozom üzerindeki
  - SNP'leri
  - Alellerin dağılımını analiz eder
- Referans kromozoma (dizomik) gerek yok
- Paternal DNA gerekir

MPS

Çalışma	N	Sonuç - %	Tr 21	Tr 18	Tr 13	XO
Rossa WK, 2011	753	8,7	%100(86/86)			
Palomaki GE, 2011	4664	6	%98,6(209/212)			
Ehric M, 2011	480	6,7	%100(39/39)			
Palomaki GE, 2012	1971	0,9		%100 (59/59)	%91,7 (11/12)	
Bianchi DW, 2012	2882	8,9	%100(89/89)	%97,2 (35/36)	%78,6 (11/14)	%93,8 (15/16)
Bianchi DW, 2013	113 KHygr		%100(30/30)	%100 (10/10)	%75 (3/4)	%95,2 (20/21)
Dan S, 2012	11263	1,5	%100(143/143)	%100 (47/47)		
Canick JA, 2012	25 ikiz		%100(7/7)		%100(1/1)	
Toplam	23151		%99,5 (603/606)	%99,3 (151/152)	%83,8 26/31	%94,5 35/37

DANSR

Çalışma	N	Sonuç - %	Tr 21	Tr 18	Tr 13	XO
Ashoor G, 2012	400	1	%100 (50/50)	%98 (49/50)		
Sparks AB, 2012	298		%100 (39/39)	%100 (7/7)		
Nicolaides K, 2012* *Düşük riskli pop.	2049	5	%100 (8/8)	%100 (2/2)		
Ashor G, 2013	1992	2,6			%80 (8/10)	
Norton ME, 2012	3228	4,6	%100 (81/81)	97,4 (37/38)		
Toplam	7967		%100 (178/178)	%97,9 (95/97)	%80 (8/10)	

SNP

Çalışma	N	Sonuç - %	Tr 21	Tr 18	Tr 13	XO	XXY	Triploidi
Zimmermann B, 2012	166	12,6	%100 11/11	%100 3/3	%100 2/2	%100 2/2	%100 2/2	
Nicolaides KH, 2013	242	5,4	%100 25/25	%100 3/3	%100 1/1	%100 2/2		%100 1/1
Toplam	408		%100 36/36	%100 6/6	%100 3/3	%100 4/4	%100 2/2	%100 1/1

Sonuçlar

Table 1 **Overview of large-scale validation studies for NIPT for Down syndrome**

	No. of samples	T21 samples	NGS platform	Whole genome (WG)/Targeted (T) approach	Number of mapped reads per sample	Sensitivity (%)	Specificity (%)
Ehrich 2011[12]	449 (4-plex)	39	Illumina GAIIx	WG	3–5 million	100	99.7
Chiu 2011[11]	2-plex $n=314$ 8-plex $n=753$	86	Illumina GAIIx	WG	2.3 million (2-plex) 0.3 million (8-plex)	100 (2-plex) 79.1 (8-plex)	97.9 (2-plex) 98.9 (8-plex)
Palomaki 2011[14]	4664 (4-plex)	212	Illumina High Seq 2000	WG		98.6	99.8
Sparks 2012[26]	298	39	Illumina High Seq 2000	T		100	100
Sparks 2012[24]	163	35	Illumina High Seq 2000	T			
Ashoor 2012[27]	397	50	n.s.	T		100	100
Norton 2012[28]	3228	81	n.s.	T		100	99.7
Bianchi 2012[31]	2882 (6-plex)	89	Illumina High Seq 2000	WG	n.s.	100	100

Tr 21

%98.9-100 (%99,3)

NIPT, noninvasive prenatal testing; NGS, next-generation sequencing; n.s., not specified.

Prenatal Diagnosis 2013, **33**, 563–568

DOI: 10.1002/pd.4111

PRENATAL **DIAGNOSIS**

REVIEW

Benefits and limitations of whole genome versus targeted approaches for noninvasive prenatal testing for fetal aneuploidies

Elles M. J. Boon[1]* and Brigitte H. W. Faas[2]

Sonuçlar

DOI: 10.1002/pd.4109 PRENATAL **DIAGNOSIS**

REVIEW

Fetal aneuploidy detection by maternal plasma DNA sequencing: a technology assessment

Judith M. E. Walsh[1]* and James D. Goldberg[2]

Table 4 **Results of studies using cell-free fetal DNA to screen for fetal aneuploidy**

Author, year	*N* total	*N* with abnormal karyotype	Main results: T21	Main results: T18	Main results: T13	Comments
Palomaki, 2011[10] Palomaki, 2012[11]	1971	212 (T21) 59 (T18) 12 (T13)	98.6% detection rate 99.8% specificity	100% detection rate 99.72% specificity	91.7% detection rate 99.03% specificity	Overall detection rate 98.9% for common aneuploidies 17 samples could not be interpreted: three were T18 Very few T13 cases
Sehnert, 2011[12]	119	53	100% sensitivity	100% sensitivity	N/A	Training and validation set: Training set – 71 samples (26 abnormal karyotypes) and validation set – 48 samples (27 abnormal karyotypes) 13 T21 and 8 T18 samples
Ehrich, 2011[13]	480	39	100% sensitivity	N/A	N/A	Only 39 T21 samples
MELISSA Bianchi, 2012[14]	532	221 Total 89 (T21) 36 (T18) 14 (T13)				No false positives for autosomal euploides
Chiu, 2011[9]	753	86				Two different methods tested (two-plex and eight-plex). two-plex method had better sensitivity
Ashoor, 2012[15]	400	100 50 (T21) 50 (T18)				Specificity calculated on a total of 300 euploid fetuses, although three samples were not available for analysis
Sparks, 2012[6]	338	88	100% sensitivity	100% sensitivity	N/A	36 T21 cases in validation set Seven T18 cases in validation set
NICE Norton, 2012[8]	3228	119 81 (T21) 38 (T18)	100% sensitivity (95% CI = 95.5–100%) False-positive rate 0.03% (95% CI = 0.002–0.20%)	97% sensitivity (95% CI = 86.5–99.9%) False-positive rate 0.07% (95% CI = 0.02–0.25%)	NA	4.6% of samples were not able to be analyzed either due to low fetal DNA fraction or assay failure

N/A, not applicable; MELISSA, MatErnal Blood IS source to Accurately diagnose fetal aneuploidy; NICE, Noninvasive Chromosomal Evaluation.

Tr21	Tr18	Tr13
%99,3	%97,4	%78,9

Istanbul Tıp/Premed

N	Endikasyon	cffDNA	Sitogenetik
1	IAY	Tr21	Tr21
2	IAY	Monozomi X	Normal
3		Monozomi X	Monozomi X
4	IAY+1trim+patUS	Tr21	Tr21
5	IAY+1trim	Tr13	Normal
6	IAY	XXY	Normal
7	IAY+1 trim+patUS	Tr21	Tr21
8	IAY+PatUS	Tr18	Tr18
9		Tr21	Tr21
10		Tr21	Tr21
11		XXY	Normal
12	NT	Tr21	46,der(21q;21q),+21
13	NT	Tr21	Tr21

Diğer sendromların tanısı

Sendrom	Bölge	Delesyon alanı	Görülme sıklığı
22q	22q11	3Mb	1/4,000
Cri-du-chat	5p	5-40Mb	1/50,000
Angelman	15q	5-6Mb	1/20,000
Prader-Willi	15q	5-6Mb	1/20,000
1p36	1p	1.5-10Mb	1/10,000
Trisomi 16	Krom 16	NA	1/50,000
Trisomi 22	Krom 22	NA	1/40,000

NIPT: Non İnvazif Prental Test

- Diagnostik olmasa bile çok güçlü bir tarama metodu
  - FPR:<%1 DR:>%99
- Operatöre bağımlı değil
- Erken yapılabilir (> 10 hf)
- Kabul edilme oranı yüksek
- İnvazif değil
- İnvazif girişim gereksinimini azaltıyor
  - Fetal kayıp riski az
  - Anksiyete az

- Sadece Tr 21,13,18, (+ send.)
- AS ile konfirmasyon gerekli
- Yetersiz fetal fraksiyon (< %4)
- Plasental-mozaisizm riski
- Çoğul gebelikler
- "Vanishing twin"
- Maternal aneöploidi
- Maternal malignite

- Klinik çalışmalar?
- **Fiyat**
  - Cihaz ve biyoenformatik pahalı
  - Zor (her yerde yapılamıyor)
- Az sayıda araştırmacı ve firmanın tekelinde

Kime NIPT

ACOG

Box 1. Indications for Considering the Use of Cell Free Fetal DNA ⇦

- Maternal age 35 years or older at delivery
- Fetal ultrasonographic findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen.
- Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

Türkiye

Maternal Kanda Hücre Dışı Fetal DNA (cffDNA) ile "Non-Invasive Prenatal Test (NIPT)"

Uzman Görüşü

Raporu onaylayanlar *(soyadı sırasına göre)*; BAKSU Başak, BAŞARAN Seher, BAŞGÜL Alin, BATUKAN Cem, ERMİŞ Hayri, GEDİKBAŞI Ali, GÜL Ahmet, HAS Recep, KALELİOĞLU İbrahim, PEKİN Oya, POLAT İbrahim, ŞAHİNOĞLU Zeki, ULUDOĞAN Mehmet, TUĞRUL Semih, YAZICIOĞLU Fehmi, YILDIRIM Gökhan, YÜKSEL Atıl)

Yayınlanma tarihi*: Mart 2013, TJOD İstanbul Şubesi*

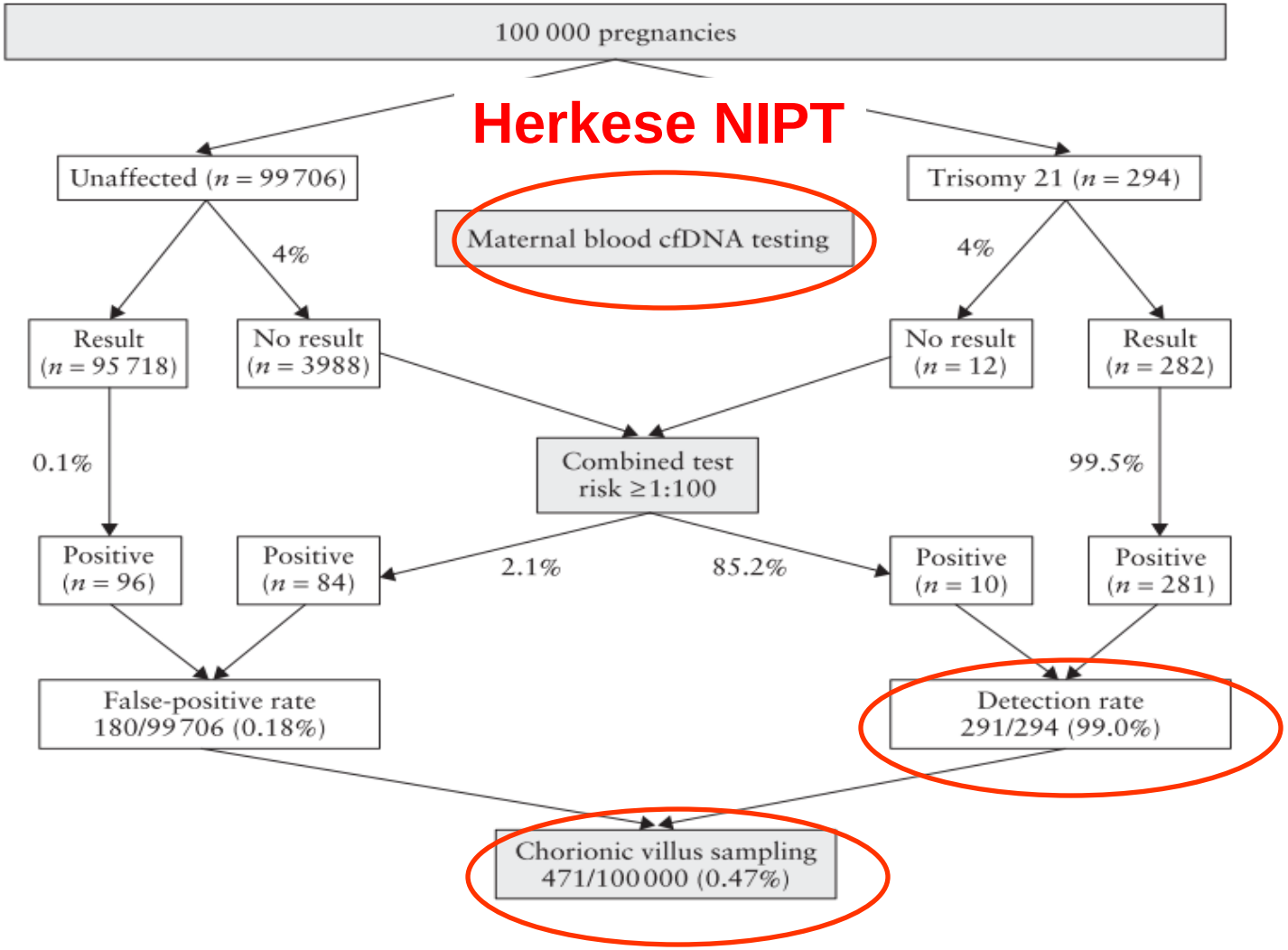
cffDNA ile NIPT'nin olası kullanım alanları:

- ✓ **Maternal yaşın 35 ve üstünde olması.**
- ✓ **Trizomi 21 ve 18'li fetus / bebek doğumu öyküsünde.**
- ✓ **Trizomi tarama testlerinin pozitif olması durumunda.**
- ✓ **Parental dengeli robertsonian Trizomi 21 ve Trizomi 13 translokasyonu.**

Ultrasound Obstet Gynecol 2013; **42**: 41–50
Published online 7 June 2013 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.12511

First-trimester contingent screening for trisomy 21 by biomarkers and maternal blood cell-free DNA testing

K. H. NICOLAIDES*†, D. WRIGHT‡, L. C. POON*, A. SYNGELAKI* and M. M. GIL*



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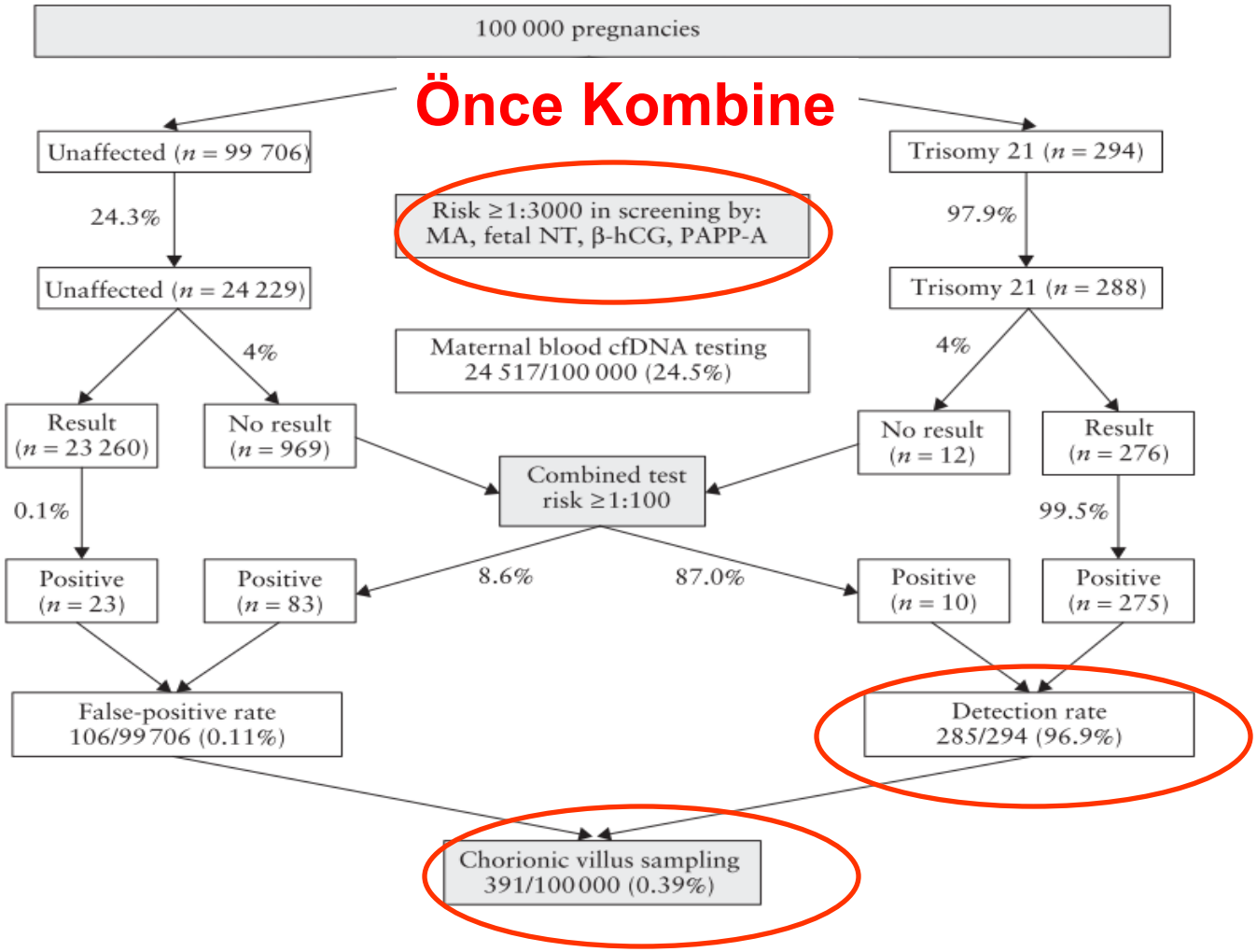

NIPT

- Çok düşük riskli gruba önerilmiyor
  - Maliyet
- **"İkinci basamak tarama testi"**
  - **DR >%99**
  - **FPR <%1**
  - NIPT (+) >invazif

- Çok yüksek riskli gruba önerilmiyor
  - Artmış NT
  - Trans/Del taşıyıcı ebeveyn
  - Fetal anomaliler
    - Omfalosel
    - Holoprozoensefali
    - Megasist
    - Diafragma hernisi, vs

Gelecek?

- Düsük riskli populasyonda rutin tarama
- Çogul gebelikler
- Diğer kromozomal anomaliler
- Sub-kromozomal anormallikler
- cfDNA ve gebelik komplikasyonlari
- Genetik sendromlarin (Down) tedavisi

Table 2 **Currently available cell-free DNA tests used to screen for fetal aneuploidy**

Company	LDT name	Trisomy identified			Testing approach	
		T21 (Down syndrome)	T18 (Edwards syndrome)	T13 (Patau syndrome)	Directed analysis	Random sequencing (MPSS)
Ariosa Diagnostics	Harmony™ Prenatal Test	X	X		X	
Sequenom	MaterniT21™	X	X	X		X
Verinata Health	verifi™ prenatal test	X	X	X		X

LDT, laboratory developed test; MPSS, massively parallel signature sequencing.

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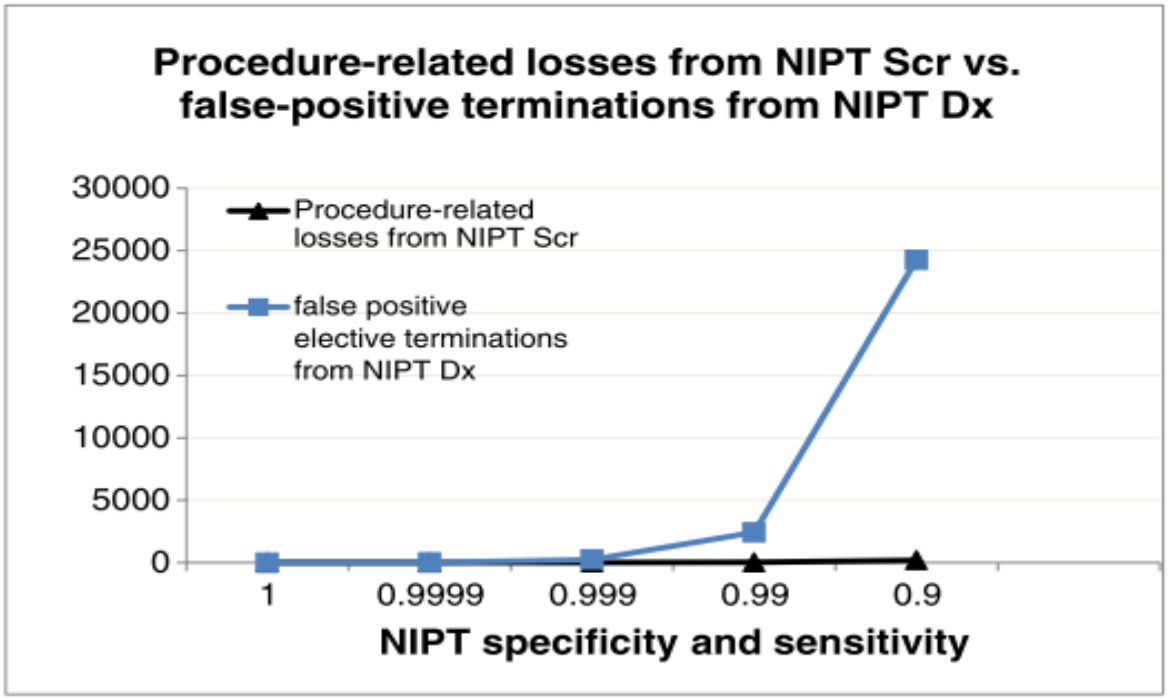

Figure 3 Comparison of false-positive (non-Down syndrome) elective terminations with noninvasive prenatal testing as a diagnostic tool (NIPT Dx) vs. procedure-related losses with NIPT Scr

Table 4 **Comparison of the adverse outcomes from noninvasive prenatal testing used as a diagnostic versus noninvasive prenatal testing used as a screening tool**

		NIPT Dx		NIPT Scr	
Specificity	Sensitivity	TAB, total	TAB, no Down syndrome	Amniocentesis	Procedure-related loss
1.0	1.0	1463	0	2184	11
0.9999	0.9999	1487	24	2220	11
0.999	0.999	1704	242	2544	12
0.99	0.99	3873	2424	5780	29
0.9	0.9	25 559	24 241	38 147	191

NIPT Dx, noninvasive prenatal testing as a diagnostic tool; NIPT Scr, noninvasive prenatal testing used for screening; TAB, elective termination.

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Table 2 **Summary of outcomes of noninvasive prenatal testing as a diagnostic tool versus noninvasive prenatal testing used for screening (per 520 000 high-risk women)**

Parameter	NIPT Dx	NIPT Scr
Down syndrome babies born	1175	1172
Amniocentesis	0	5780
Elective terminations	3873	1441
Terminations with Down syndrome	1449	1441
Terminations without Down syndrome	2424	0
Procedure-related loss	0	29
Spontaneous abortions	497	496

NIPT Dx, noninvasive prenatal testing as a diagnostic tool; NIPT Scr, noninvasive prenatal testing used for screening.

Table 3 **Summary of costs and quality-adjusted life years of noninvasive prenatal testing as a diagnostic versus noninvasive prenatal testing used for screening (per 520 000 high-risk women)**

Parameter	NIPT Dx	NIPT Scr
Costs	$1 309 000	$1 312 000
QALYs	13.955573 million	13.955973 million
	Less expensive, less effective	More expensive, more effective
Incremental cost-effectiveness ratio ($/QALY)		$7687 (compared with NIPT Dx)

NIPT Dx, noninvasive prenatal testing as a diagnostic tool; NIPT Scr, noninvasive prenatal testing used for screening; QALY, quality-adjusted life years.

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Table 1 Patient demographics and NIPT performance statistics

	Palomaki et al. [38]	Palomaki et al. [33]	Bianchi et al. [32]	Norton et al. [36]
Subjects enrolled (*N*)	4,664	4,664	2,882	4,002
Analyzed samples (*N*)	1,696	1,988*	532	3,007
Trisomy 21 cases (*N*)	212	212	89	81
Trisomy 18 cases (*N*)		59	36	38
Trisomy 13 cases (*N*)		12	14	
Monosomy X Cases (N)			16	
Female Cases (N)			233	
Male Cases (N)			184	
Maternal age cases and controls (years) mean ± SD	37 ± 5	36.6 ± 4.9 T18	34.4 ± 6.73	35.4 ± 7.3 T21
	36.6 ± 5.1	33.3 ± 5.6 T13	35.2 ± 6.40	34.5 ± 6.1 T18
		37.6 ± 5 eupld		34.3 ± 6.3 eupld
Gestational age mean cases and controls (weeks)	15.3	14.8 T18	14.8	16.4 T21
	15.0	15.2 T13	15.1	16.2 T18
		14.7 eupld		17.0 eupld
Trisomy 21 sensitivity (%)	98.6 (95.9–99.7)	99.1 (96.6–99.9)	100 (95.9–100)	100 (95.5–100)
Trisomy 21 specificity (%)	99.8 (99.4–99.9)	99.9 (99.7–99.9)	100 (99.1–100)	99.97 (99.8–99.99)
Trisomy 18 sensitivity (%)		100 (93.9–100)	97.2 (85.5–99.9)	97.4 (86.5–99.9)
Trisomy 18 specificity (%)		99.7 (99.3–99.9)	100 (99.2–100)	99.93 (99.75–99.98)
Trisomy 13 sensitivity (%)		91.7 (61–99)	78.6 (49.2–99.9)	
Trisomy 13 specificity (%)		99.1 (98.5–99.5)	100 (99.2–100)	
Female sensitivity (%)			99 (97.6–99.9)	
Female specificity (%)			99.5 (97.2–99.9)	
Male sensitivity (%)			100 (98–100)	
Male specificity (%)			100 (98.5–100)	
MX sensitivity (%)			93.8 (69.8–99.8)	
MX specificity (%)			99.8 (98.7–99.9)	

Numbers in parentheses are 95% confidence intervals given as %, *SD* standard deviation, *CI* confidence interval, *eupld* euploid, *MX* monosomy X

* 1695 of these samples were re-tested from original study [38]

Table 2 Comparison of commercially-available NIPTs

	Sequenom CMM®	Verinata Health®, an Illumina company	Ariosa™ Diagnostics
Chromosomes tested	21, 18, 13, XX, XY, MX, XXY, XXX, XYY	21, 18, 13 XXX, XXY, XYY, MX, X & Y are optional	21, 18, 13
Results reported as	Positive	Aneuploidy detected	High-risk (≥1 %)*
	Negative	No aneuploidy detected	Low-risk (<1 %)*
		Aneuploidy suspected/borderline value	
Gestational age at which test can be performed (weeks)	10+	10+	10+
Samples accepted for multi-fetal gestations	Yes	No	No
Samples accepted for egg donor/surrogate pregnancies	Yes	Yes	No
Turn-around time	8–10 days	8–10 days	8–10 days

* Risk score included

MX monosomy X

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Table 1 Eleven cell-free DNA studies of shotgun or targeted sequencing: methodological differences

Trial	*Design*	*Average GA (weeks)*	*Method*	*Algorithm*	*Cut-off**
High risk					
Chiu *et al.*[65]	Prospective and case–control	13	Shotgun	*z*-score	3.0
Ehrich *et al.*[66]	Case–control	16	Shotgun	*z*-score	2.5
Palomaki *et al.*[67,72]	Case–control	15	Shotgun	*z*-score	3.0
Bianchi *et al.*[68]	Case–control	15	Shotgun	*z*-score	4.0‡
Sparks *et al.*[70]	Case–control	18	Targeted	Risk†	1%
Ashoor *et al.*[69,75]	Case–control	13	Targeted	Risk†	1%
Norton *et al.*[71]	Prospective	16	Targeted	Risk†	1%
Other than high risk					
Lau *et al.*[73]	Prospective	14	Shotgun	*z*-score?	?
Nicolaides *et al.*[74]	Retrospective	12	Targeted	Risk†	1%
Dan *et al.*[39]	Prospective	20	Shotgun	*z*-score & L-score	2.5 or 1.0§
Gil *et al.*[78]	Prospective	10	Targeted	Risk†	1%

*For autosomal chromosomes. †Includes maternal and gestational age. ‡Results with scores 2.5–4.0 were 'unclassified'. §Positive if $z < 2.5$ but $L > 1$. GA, gestational age at testing.

be reclassified as positive, so those rates are also given in Down syndrome but depending on her pretest risk it

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we can conclude that based on present evidence cfDNA testing is not a diagnostic test of Down syndrome but rather is a very good secondary screening test. A woman with a positive cfDNA test will be at high risk of about 300-fold.

For Edwards syndrome, the overall DR is 97.4% (95% CI, 93.7–99.0%) and the FPR 0.15% (95% CI, 0.07–0.31%), with positive LR of 665 and negative

Table 2 Down syndrome and Edwards syndrome results in seven cell-free DNA studies carried out in high-risk pregnancies

	Down syndrome		*Edwards syndrome*	
Trial	*DR (n (%))*	*FPR (n (%))*	*DR (n (%))*	*FPR (n (%))*
Chiu *et al.*[65] *	86/86 (100)	3/146 (2.1)	—	—
Ehrich *et al.*[66]	39/39 (100)	1/410 (0.24)	—	—
Palomaki *et al.*[67,72]	209/212 (98.6)	3/1471 (0.20)	59/59 (100)	5/1688 (0.30)
Bianchi *et al.*[68]	89/90 (98.9)	0/410 (0.00)	35/38 (92.1)	0/463 (0.00)
Sparks *et al.*[70]	36/36 (100)	1/123 (0.81)	8/8 (100)	1/123 (0.81)
Ashoor *et al.*[69]	50/50 (100)	0/297 (0.00)	49/50 (98.0)	0/297 (0.00)
Norton *et al.*[71]	81/81 (100)	1/2888 (0.03)	37/38 (97.4)	2/2888 (0.06)
Total	590/594 (99.3)	9/5745 (0.16)	188/193 (97.4)	8/5459 (0.15)

*2-plex and 8-plex data were reported but only the more favorable 2-plex results are included here. DR, detection rate; FPR, false-positive rate.

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