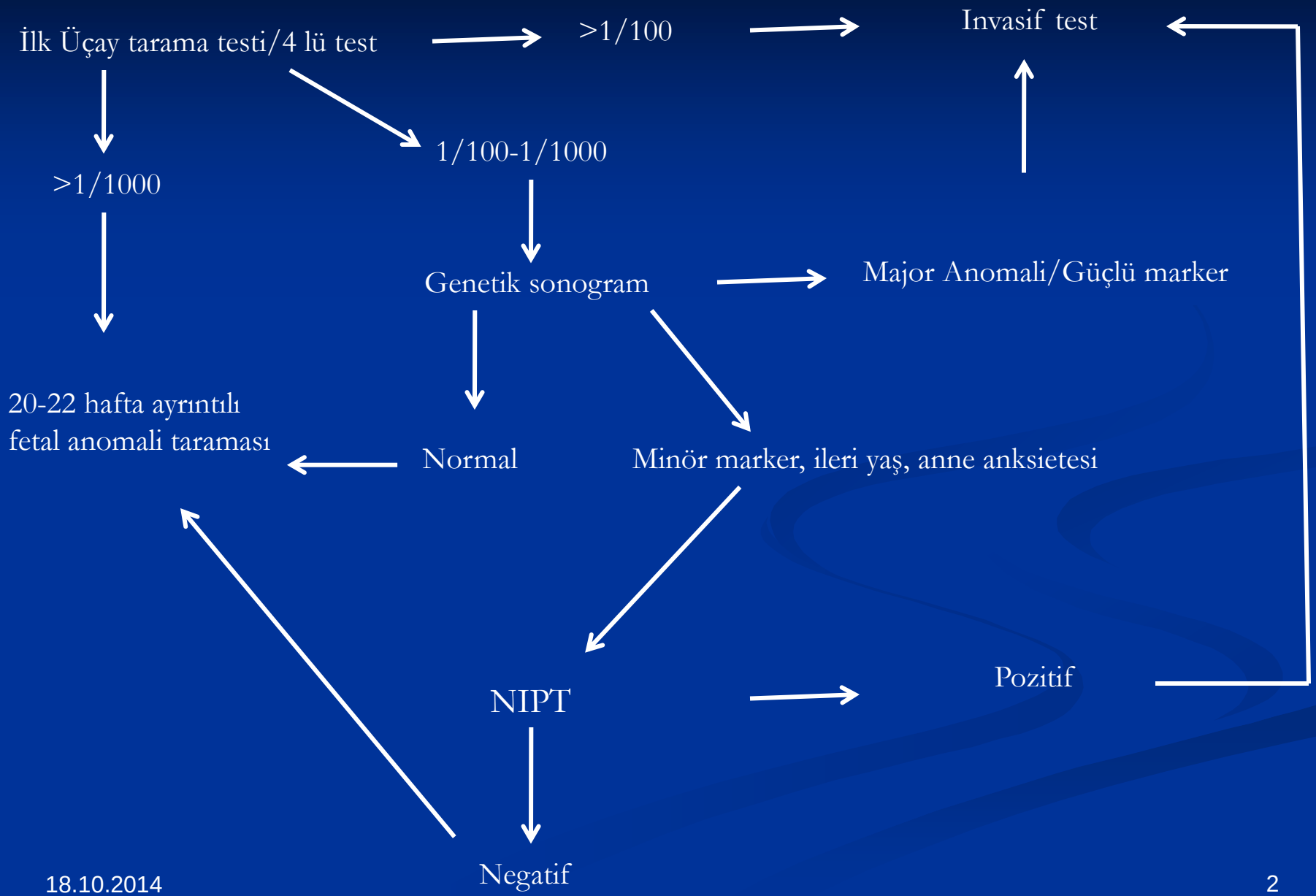
NIPT güncel T 21 tarama protokollerine nasıl entegre edilmeli

Dr. H. Fehmi Yazıcıoğlu
Perinatolog


İlk Üçay tarama testi/4 lü test
>1/100
Invasif test
>1/1000
1/100-1/1000
Genetik sonogram
Major Anomali/Güçlü marker
20-22 hafta ayrıntılı
fetal anomali taraması
Normal
Minör marker, ileri yaş, anne anksietesi
NIPT
Pozitif
Negatif

Tanı testleri komplikasyonları

- Amniyosentez / Kordosentez
- %0.5-1 fetal kayıp
- %0.001-2 maternal kayıp

- T 21 prevalans 1/800
  - T 21/fetal kayıp: 1/8
  - T 21/maternal kayıp: 60/1

Maternal mortalite

- Türkiyede 5 AS 1 FR sonrası 6 maternal kayıp
- Dünyada bildirilen 5 vaka(1'i Türkiye'den)
- Tek insidans rakamı 1/20000

Proceedings of the National Institute of Child Health and Human Development Consensus Confereence on Antenatal Diagnosis. Dec 1979, NIH Publication No:80-1973

A. Milunsky & J Milunsky Genetic disorders and the fetus: Diagnosis, Prevention and Treatment. John Wiley &Sons 2011 6th Ed.

PPV vs T21/Fetal kayıp

- Maternal yaş : %2…(2/1)
- Üçlü test: %4……..(4/1)
- Kombine test: %6…(6/1)
- NIPT: %66…… (66/1)

NIPT ile fetal kayıp oranında >10 kat azalma olur
Yakalama oranında azalma beklenmez

Klasik tarama testleri

	Anne Yaşı	Üçlü T	Dörtlü T	NT	Kombine	Entegre
SURUSS	30	70	80	62	85	93
FASTER	30	68	78	68	85	95

11-14 şarta bağlı(contingency)

- Kombine risk:
  - >1/100 …..CVS
  - 1/100 > 1/1000
    - Burun kemiği
    - Ductus venozus
    - Trikuspit regurjitasyonu
    - Yüz açısı
  - <1/1000….Takip

Yakalama oranı: %95
Yanlış pozitif oranı:%2.5

Yakalama oranı: %98
Yanlış pozitif oranı:%5

Amaç: Fetal kayıp oranının azaltılması

- NIPT yüksek riskli gruba uygulanmalı:
  - >35
  - Pozitif aneuploidi anamnezi
  - Pozitif tarama testi
  - Pozitif genetik sonogram
  - Robertsonian translokasyon taşıyıcılığı

Hangisi medikolegal bir sorundur?

- İnvasif girişime bağlı fetal kayıp
- Atlanan Down sendromu

(Wrongful Birth)

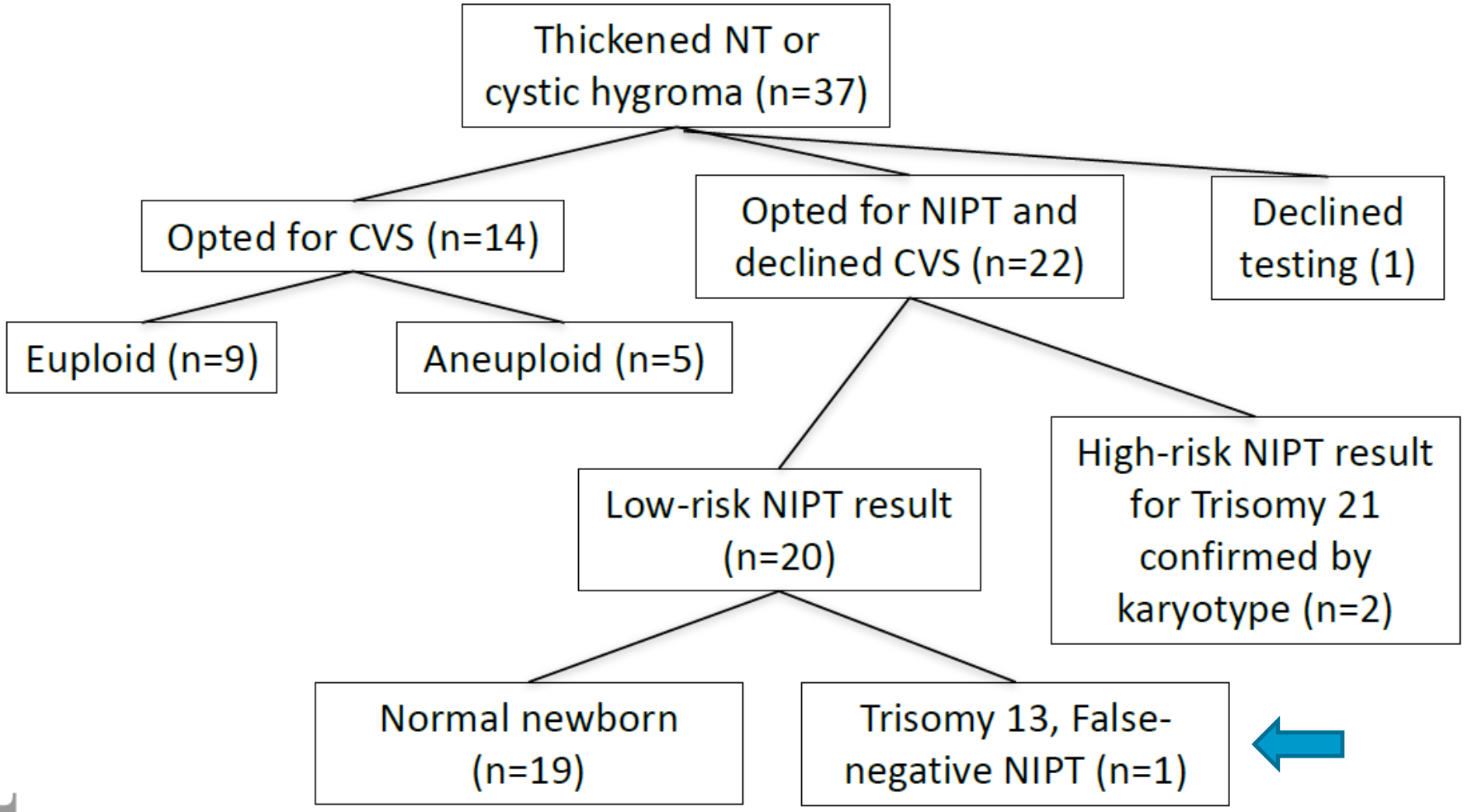
Amaç: ~%100 yakalama oranı

- Herkese 10. haftadan itibaren NIPT

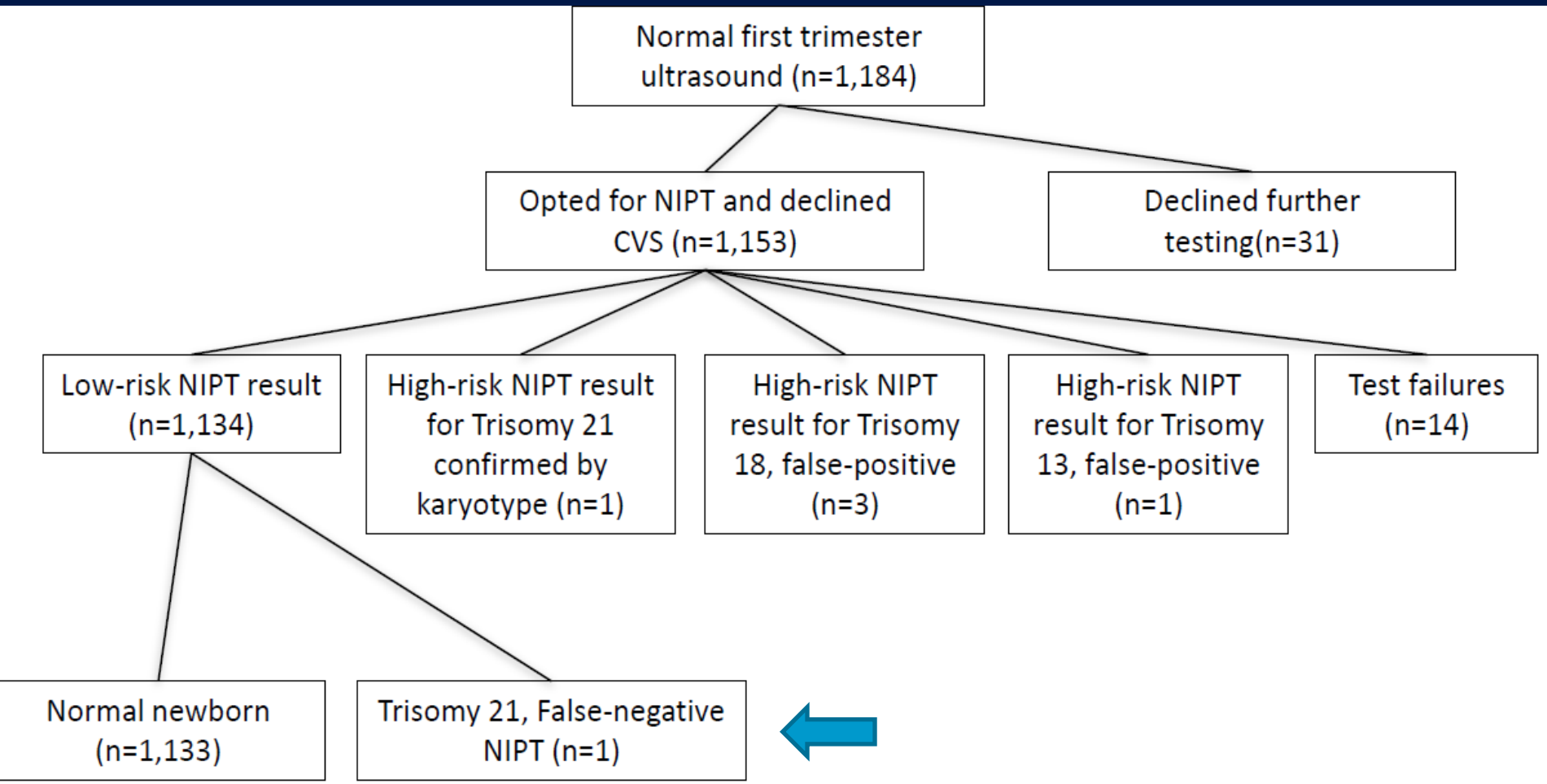
  - Düşük riskli popülasyonda yeterli validasyon çalışması yok
  - FDA onayı yok
  - Atipik kromozomal anomaliler atlanır
  - PAHALI

Studie	Euploid		Trisomie 21	
	n	Falsch-Positiv-Rate	n	Detektionsrate
		% (n)		% (n)
Studien im Risikokollektiv				
Norton et al. [18]	2888	0,03 % (1)	81	100 % (81)
Palomaki et al. [20]	1471	0,2 % (3)	212	98,6 % (209)
Bianchi et al. [11]	410	0 % (0)	90	98,9 % (89)
Ehrich et al. [69]	410	0,24 % (1)	39	100 % (39)
Ashoor et al. [19]	297	0 % (0)	50	100 % (50)
Screeningstudien im Normalrisikokollektiv				
Nicolaides et al. [13]	1939	0 % (0)	8	100 % (8)
Song et al. [70]	1733	0 (0)	8	100 % (8)
Dan et al. [71]	10916	0,009 % (1)	139	100 % (8)

Kagan KO et al. Combined First Trimester… Ultraschall in Med 2014; 35: 229–236



Jackson J et al. Nuchal translucency plus non-invasive prenatal testing to screen foraneuploidy in a community-based average-risk population . Acceped article Ultrasound Obstet Gynecol 2014



Jackson J et al. Nuchal translucency plus non-invasive prenatal testing to screen foraneuploidy in a community-based average-risk population Accepted article Ultrasound Obstet Gynecol 2014

NIPT / FDA

- Karmaşık yazılım ürünü
- Kullanılan otomasyon sistemi şeffaf değil
- Validasyonu henüz tam değil
- Agresif pazarlama stratejisi uygulanıyor
- Direkt tüketiciye ulaştırma çabaları dikkat çekiyor

NIPT vs Invasif Tanı

Aneuploidies identified by current prenatal screening and predicted detection by NIPT

Detectable		Not Detectable	
Aneuploidy	n (%)	Abnormality	n (%)
Trisomy 21	1592 (53.2)	Mosaicism	186 (6.2)
Trisomy 18	511 (17.1)	Other trisomies	92 (3.1)
Trisomy 13	139 (4.6)	Insertions/deletions	88 (2.9)
Sex chromosome aneuploidy	247 (8.3)	Structural abnormalities	100 (3.3)
		Balanced	97 (3.2)
		Unbal anced rearrangements	3 (0.1)
		Triploidy	29 (1.0)
		Marker chromosomes	9 (0.3)
Total	2489 (83.2)		504 (16.8)

NIPT, non-invasive prenatal testing.

Norton M et al, AJOG 2014

Strategy	CVS (n)	NIPT (n)	Estimated detection rate of: Trisomy 21 (n (DR))	Trisomy 13/ trisomy 18/sex (n (DR))	Atypical abnormal karyotype† (n (DR))	Phenotypically important abnormal karyotype (n (DR (95% CI)))
NIPT in all cases	—	193 638	500 (100)	315 (100)	—	815 (75.7 (73.0–78.1))
NIPT in all > 1:3000	—	44 391	488 (97.6)	279 (88.6)	—	767 (71.2 (68.4–73.8))
NIPT in all > 1:1000	—	19 153	467 (93.4)	251 (79.7)	—	718 (66.7 (63.8–69.4))
CVS > 1:10; NIPT 1:10 to 1:1000	734	18 419	467 (93.4)	251 (79.7)	13 (4.9)	731 (67.9 (65.0–70.6))
CVS > 1:100; NIPT 1:100 to 1:1000	4002	15 151	467 (93.4)	251 (79.7)	64 (24.4)	782 (72.6 (69.9–75.2))
CVS if one or more risk factor(s)*	5584	—	406 (81.2)	222 (69.6)	89 (34.4)	717 (66.6 (63.7–69.3))
CVS if one or more risk factor(s)* and NIPT 1:100 to 1:1000	5584	13 792	467 (93.4)	263 (83.5)	89 (34.4)	819 (76.0 (73.4–78.5))
CVS > 1:300; NIPT 1:300 to 1:1000	8018	11 135	467 (93.4)	251 (79.7)	85 (32.4)	803 (74.6 (71.9–77.1))
CVS > 1:100; no NIPT	4002	—	404 (80.8)	190 (60.3)	64 (24.4)	658 (61.1 (58.3–64.0))
CVS > 1:300; no NIPT	8018	—	436 (87.2)	234 (74.3)	85 (32.2)	755 (70.1 (67.3–72.8))

Out of 1122 abnormal karyotypes, 1077 karyotypes were phenotypically important but, of these, 262 atypical abnormal karyotypes would be missed by (NIPT). *Risk factors: trisomy 21, risk > 1:100 and/or nuchal translucency ≥ 3.5 mm and/or pregnancy-associated plasma protein-A < 0.2 multiples of the median (MoM) and/or free β-human chorionic gonadotropin < 0.2 MoM or > 5.0 MoM and/or maternal age ≥ 45 years. †Atypical abnormal karyotype, karyotype (not trisomy or sex-chromosome aneuploidy) of probable phenotypic importance, undetectable by NIPT, including unbalanced karyotypes, marker chromosomes and triploidies; DR, detection rate; sex, sex chromosome aneuploidies.

Petersen OB et al Potential diagnostic consequences of applying non-invasiveprenatal testing: population-based study from a country withexisting first-trimester screening Ultrasound Obstet Gynecol 2014; 43: 265–271

Testing strategy	Screening risk cut-off (1 in)	Cost per NIPT test	(A) Cost of screening (£000s)	(B) Cost of NIPT (£000s)	(C) Cost of invasive diagnostic tests (£000s)*	(A)+ (B)+ (C) (£000s)
DS screening using the combined test	150		200	0	79	279
NIPT as contingent testing	150	£50	200	8	6	213
	150	£250	200	39	6	244
	150	£500	200	78	6	283
	150	£750	200	116	6	322
	500	£50	200	18	6	225
	500	£250	200	91	6	298
	500	£500	200	183	6	389
	500	£750	200	274	6	480
	1,000	£50	200	30	6	237
	1,000	£250	200	149	6	356
	1,000	£500	200	298	6	505
	1,000	£750	200	448	6	655
	2,000	£50	200	46	7	253
	2,000	£250	200	230	7	438
	2,000	£500	200	461	7	668
	2,000	£750	200	691	7	898
NIPT as first-line screening		£50	0	438	11	449
		£250	0	1,642	11	1,825
		£500	0	3,535	11	3,546
		£750	0	5,255	11	5,266

69% uptake of DS screening using the combined test. 80% uptake of NIPT as contingent screening for unaffected pregnancies and 90% for affected. pregnancies. 69% uptake of NIPT as first-line screening.

*Including procedural miscarriages. DS = Down's syndrome; NIPT = non-invasive prenatal testing

doi:10.1371/journal.pone.0093559.t004

Amaç: En düşük maliyet ile mümkün olan en yüksek yakalama oranı/en düşük yanlış pozitiflik

- Klasik tarama metodlarına NIPT entegrasyonu

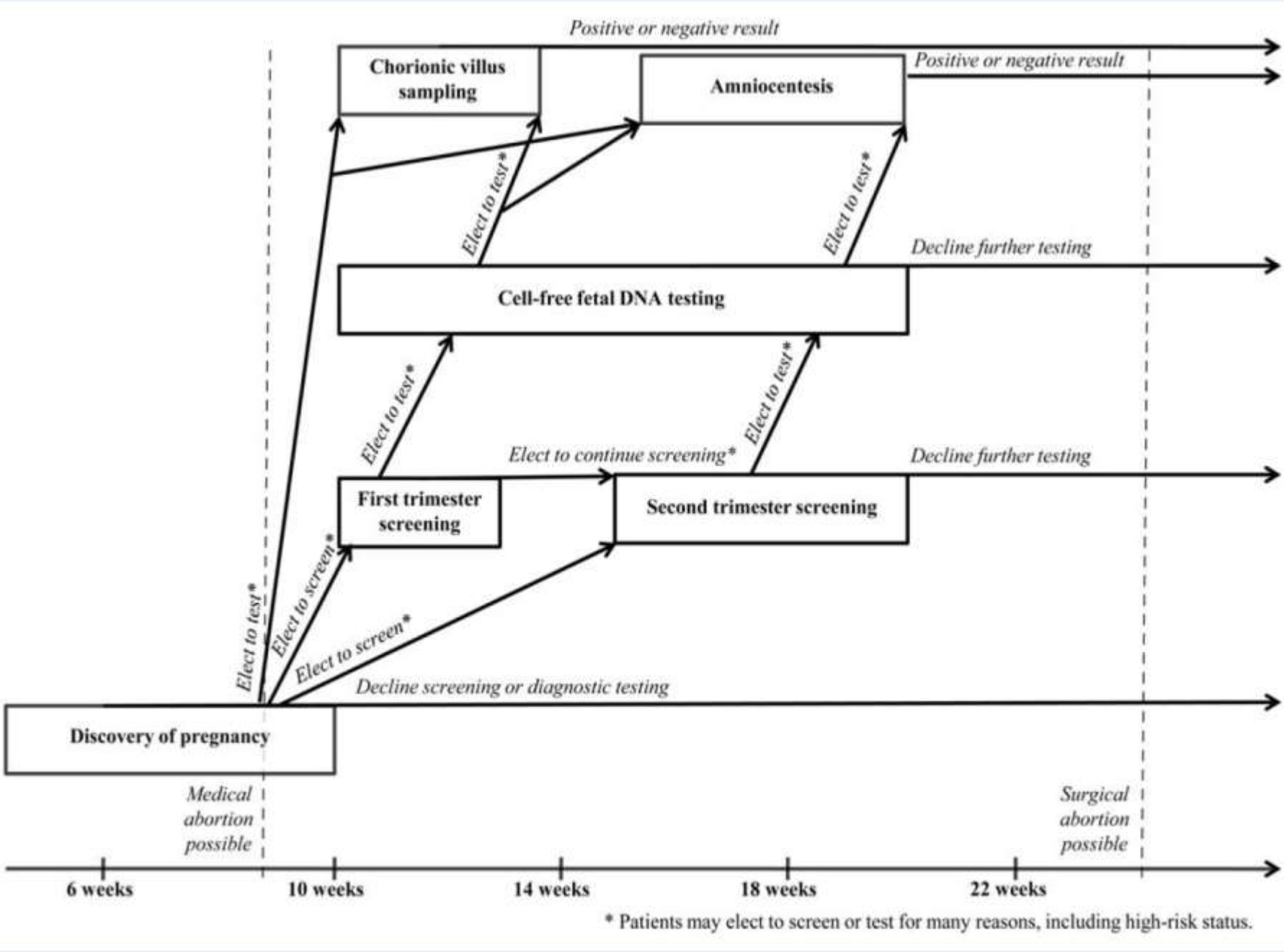
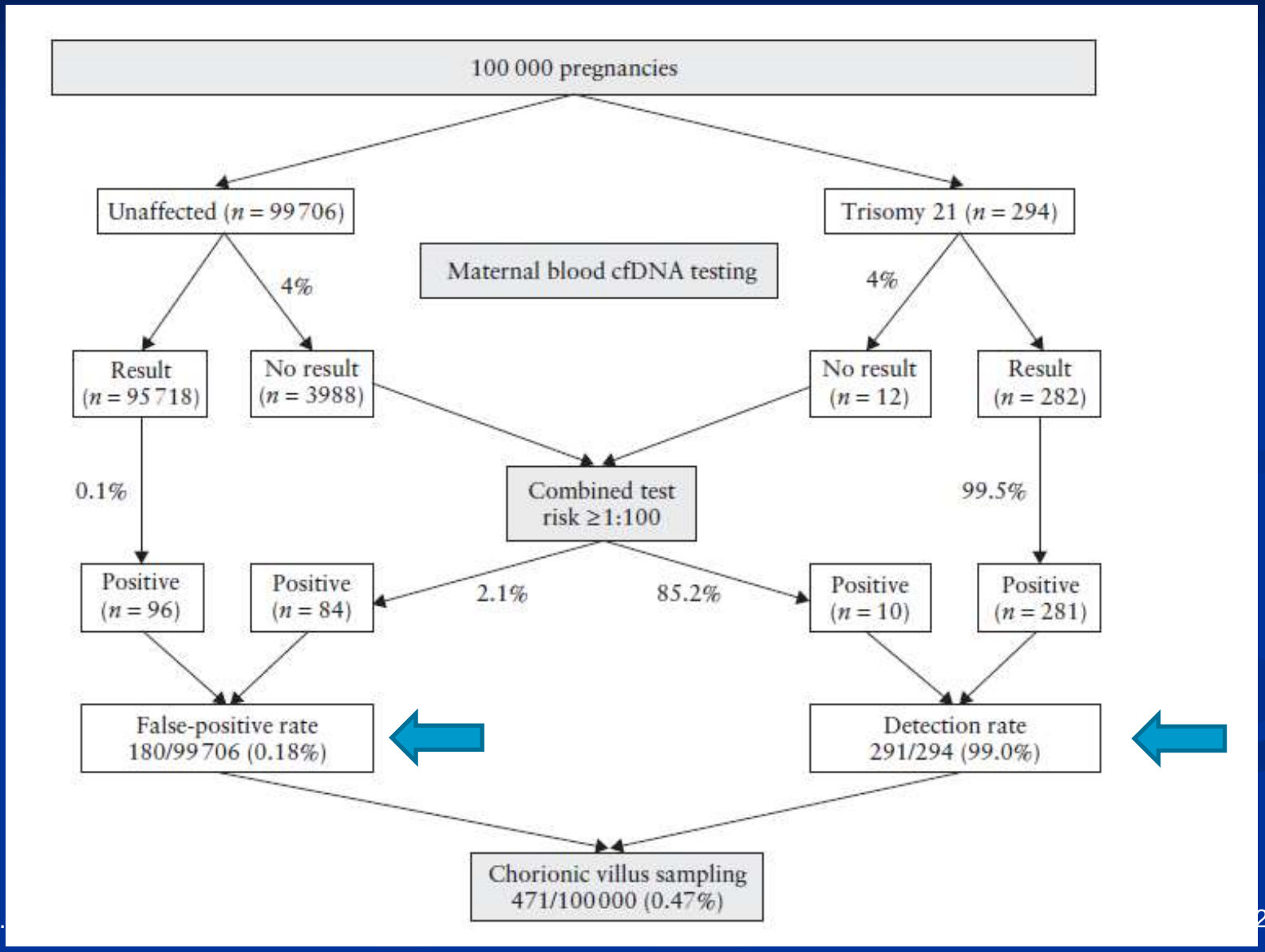
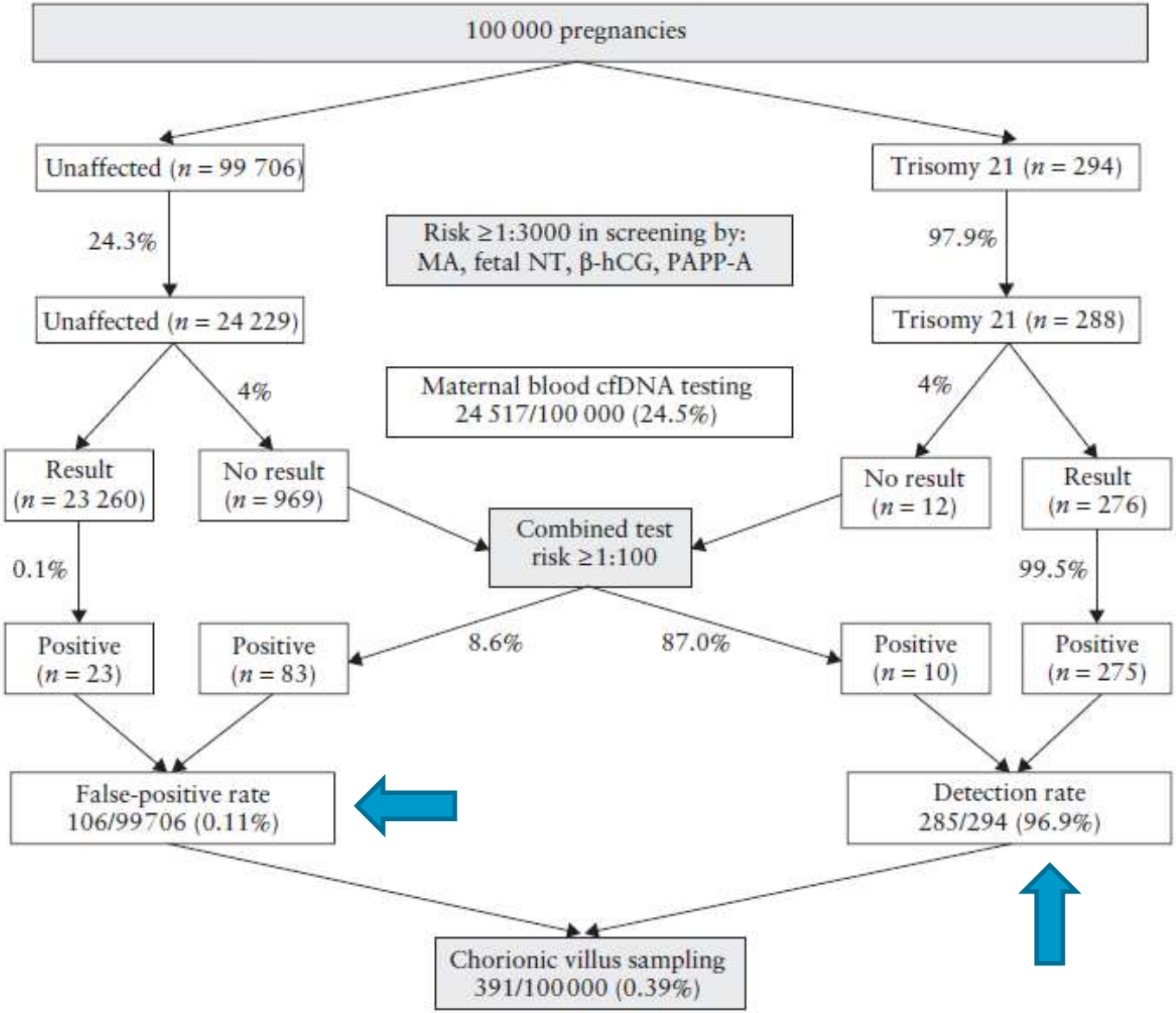


Figure 1 Prenatal screening and testing schematic incorporating cffDNA testing.

King's College modeli



King's College modeli



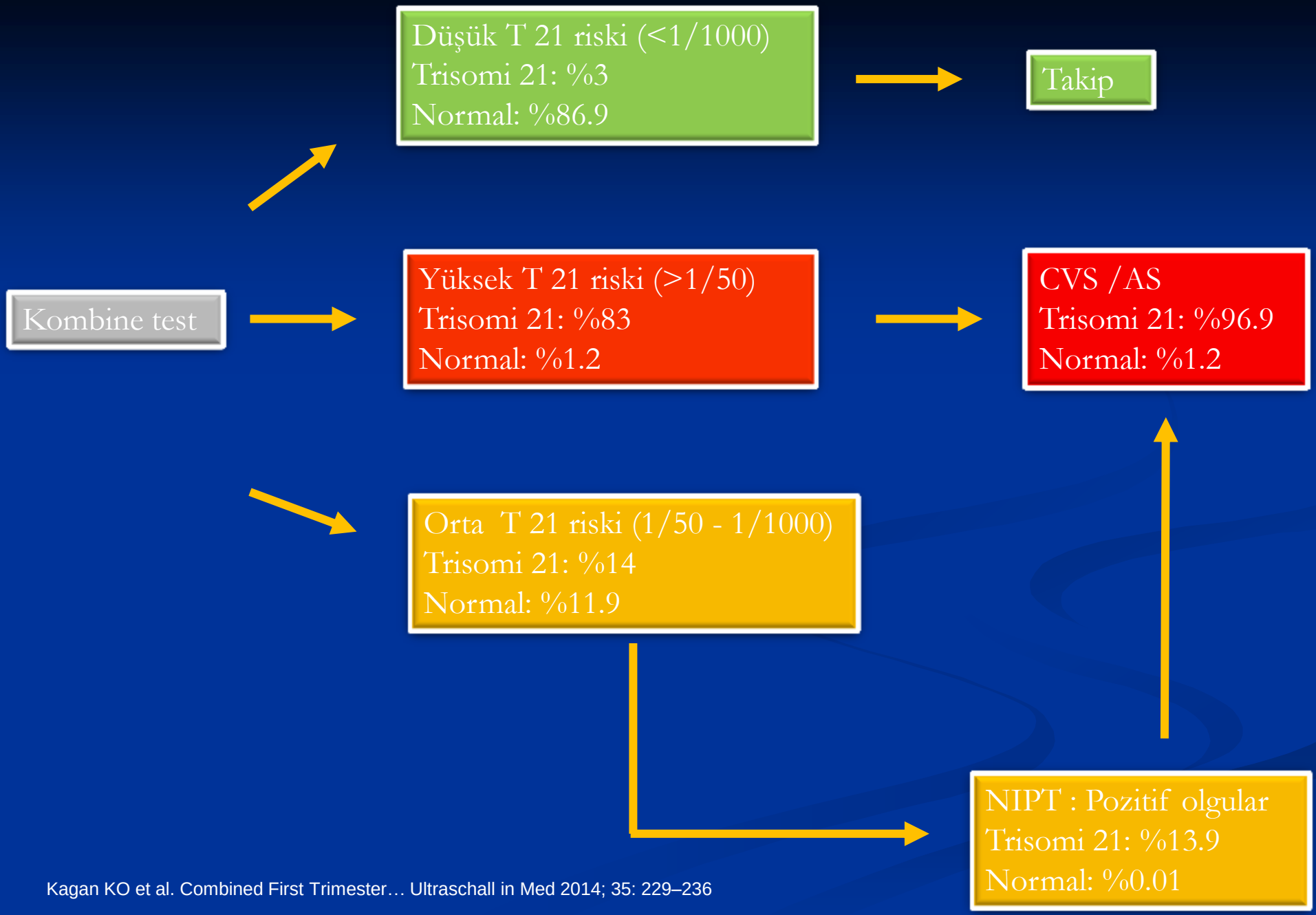
Avustralya modeli

- Kombine risk:
  - >1/10……...CVS
  - 1/10 -1/1000….NIPT
  - <1/1000……Takip
- CVS: %0.8
- NIPT:% 13
- DR:>%98

Hui L et al Aust NZJ Obstet Gynaecol 2013

Israil Modeli

- 10. haftada herkese cffDNA
- cffDNA (+)…..CVS
- 14-16 haftada ayrıntılı USG
  - Strüktürel anomaliler
  - Preeklampsi
  - Erken doğum



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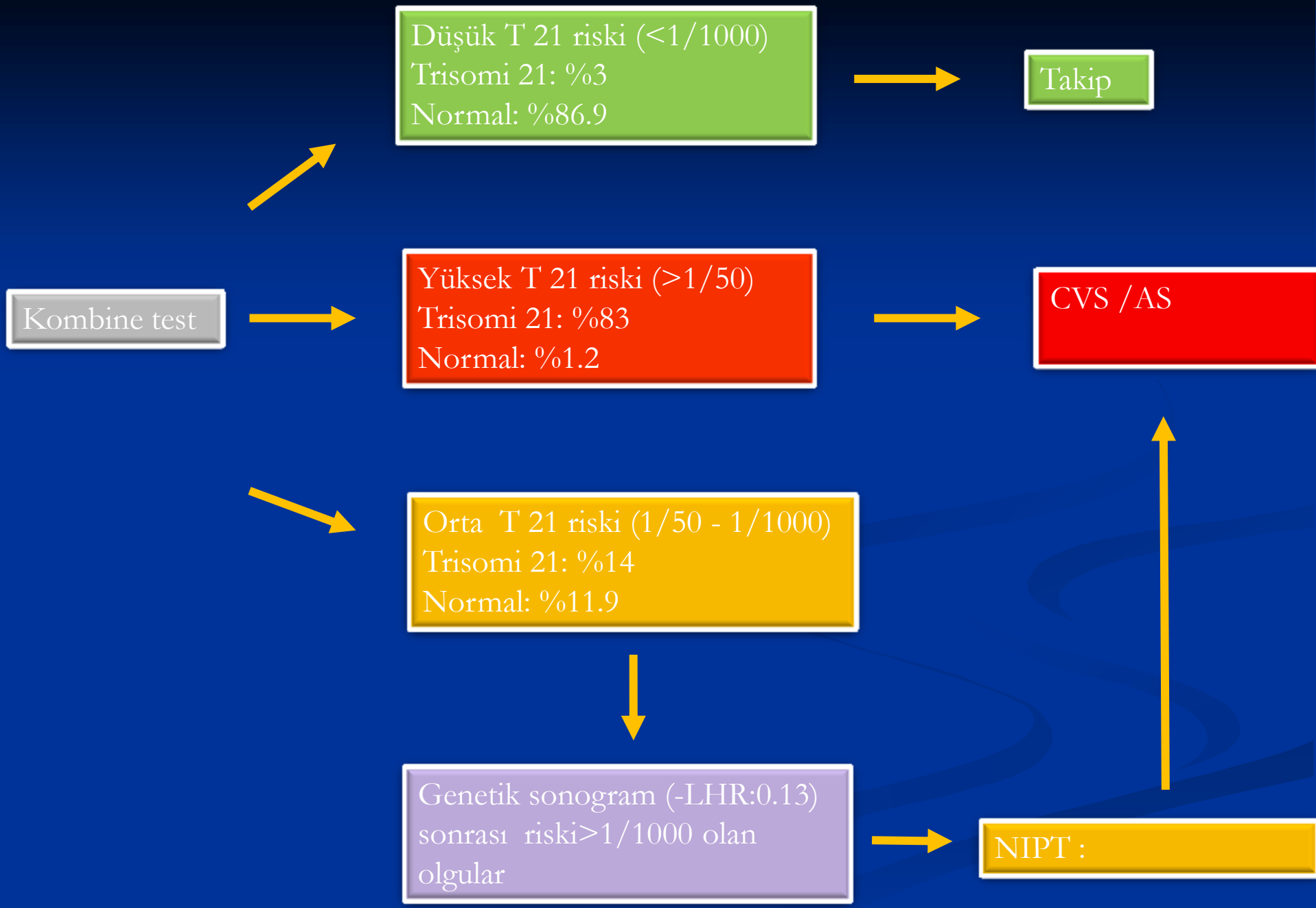
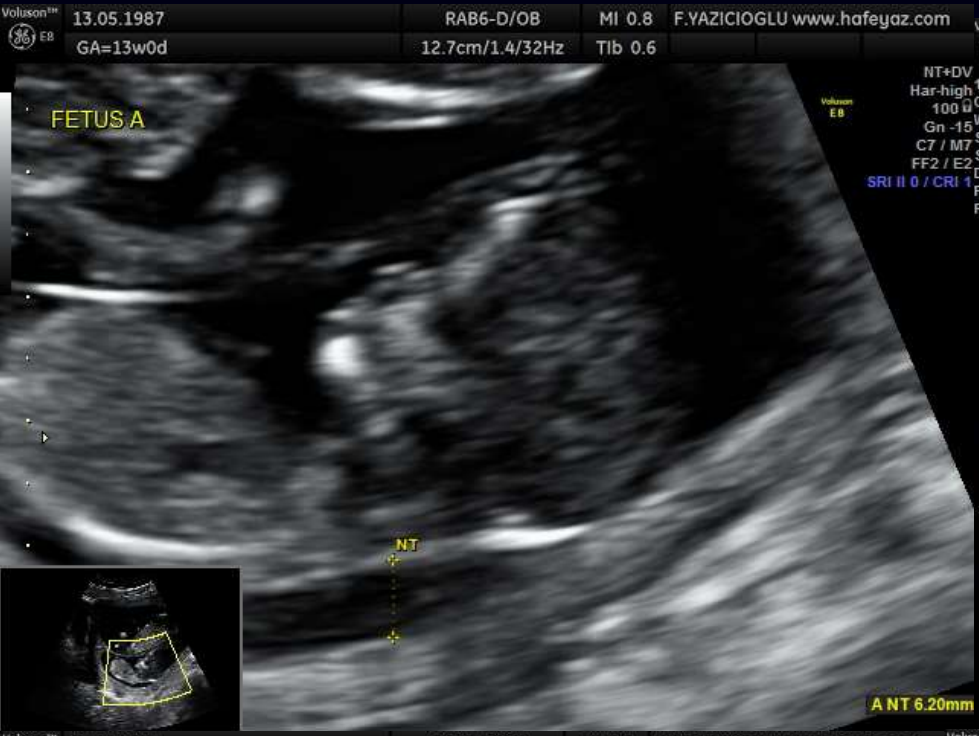
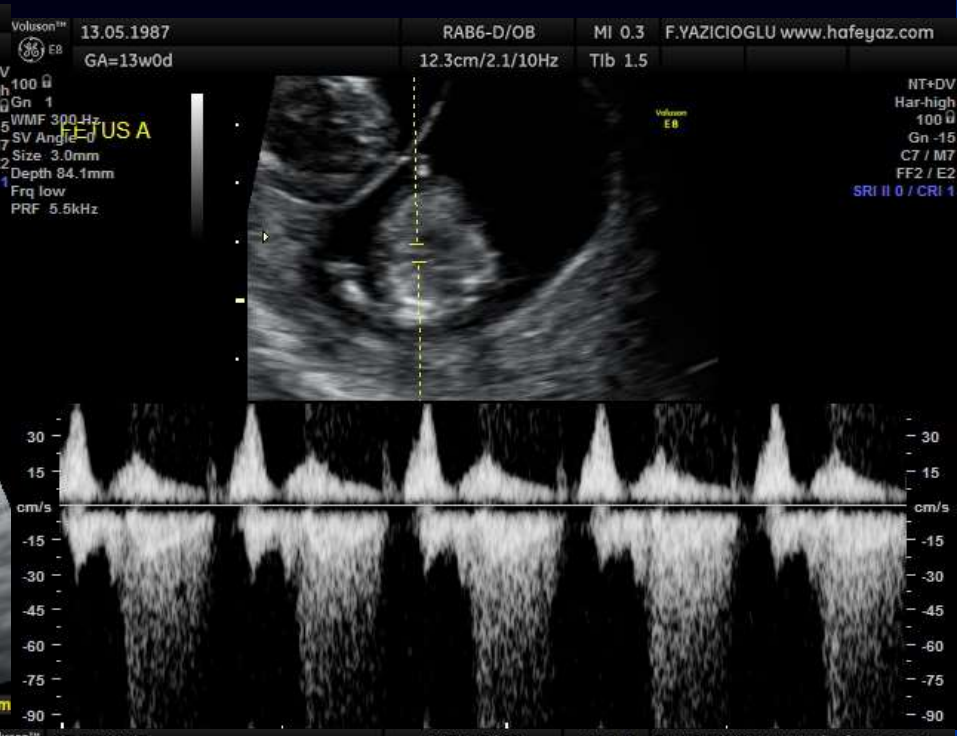
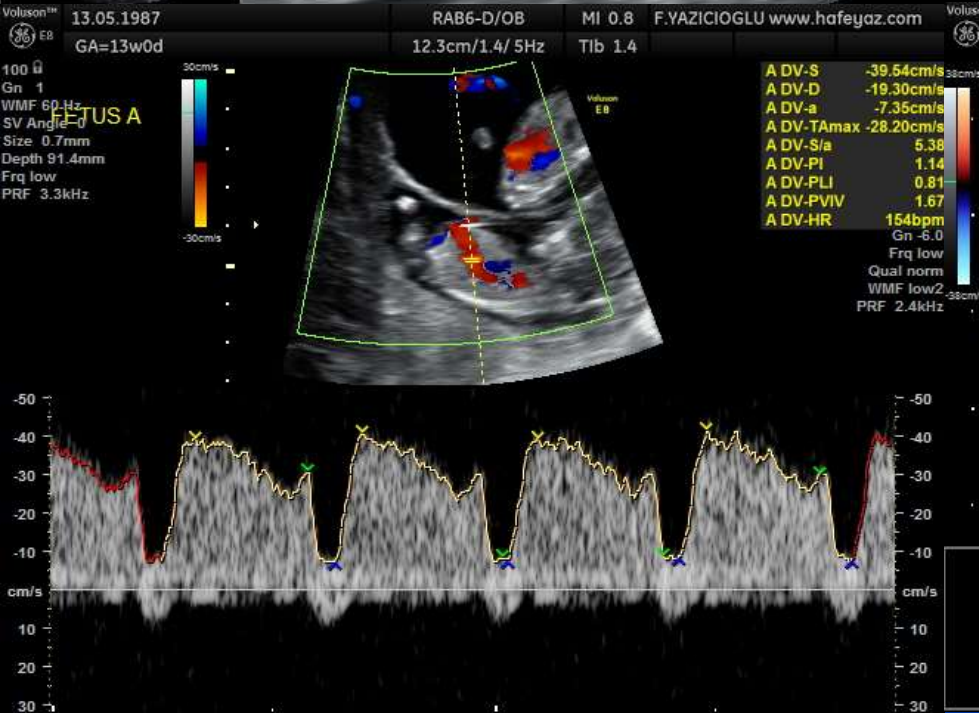

Düşük T 21 riski (<1/1000)
Trisomi 21: %3
Normal: %86.9
Takip
Kombine test
Yüksek T 21 riski (>1/50)
Trisomi 21: %83
Normal: %1.2
CVS /AS
Orta T 21 riski (1/50 - 1/1000)
Trisomi 21: %14
Normal: %11.9
Genetik sonogram (-LHR:0.13) sonrası riski>1/1000 olan olgular
NIPT :

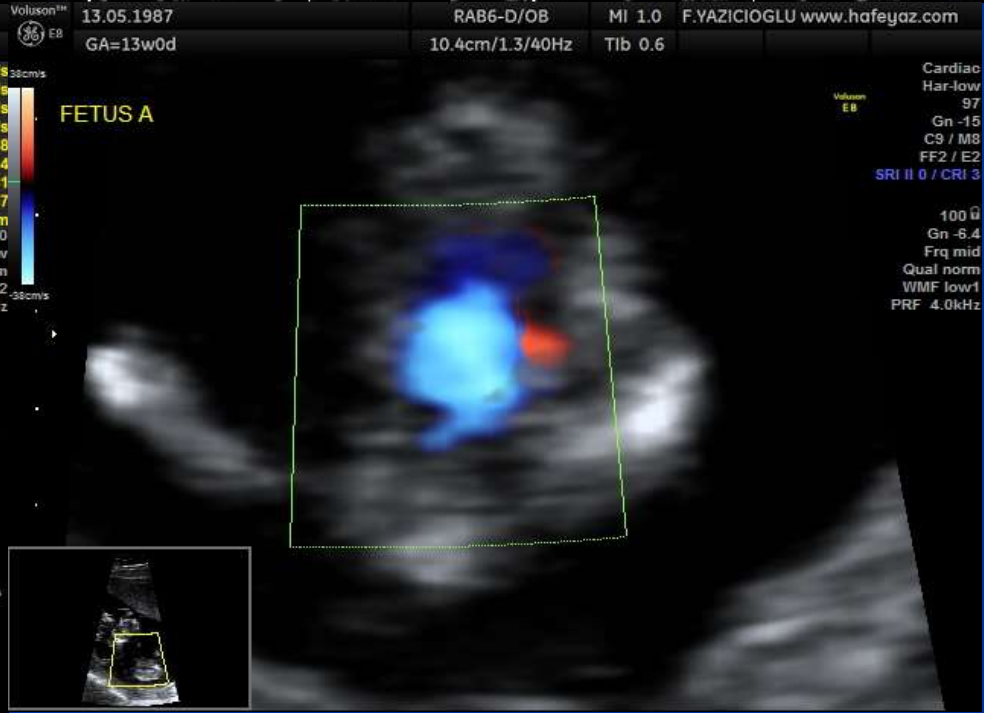
Farklı model önerisi

- Kombine test T 21 risk:
- >1/50…..CVS
- <1/50…Genetik sonogram(-LHR:0.13)
- Post GS risk:
- >1/50….AS
- 1/50-1/3000…NIPT
- <1/3000…Takip

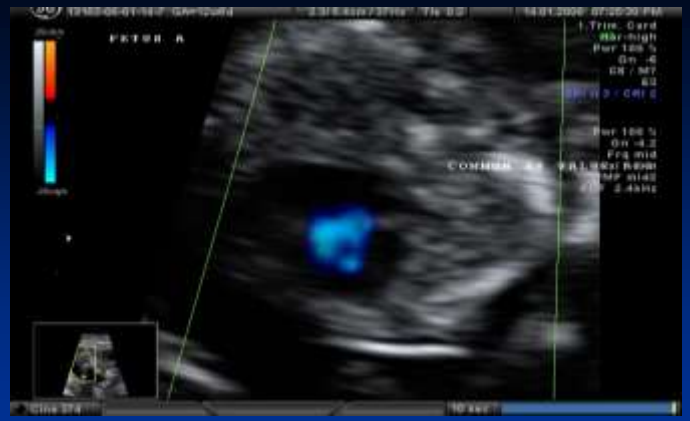

13.05.1987
RAB6-D/OB
MI 0.8
F.YAZICIOGLU www.hafeyaz.com
GA=13w0d
12.7cm/1.4/32Hz
TIb 0.6
FETUS A
NT
A NT 6.20mm

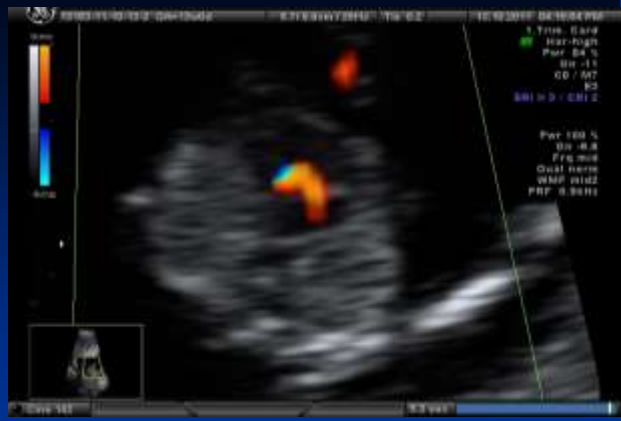

13.05.1987
RAB6-D/OB
MI 0.3
F.YAZICIOGLU www.hafeyaz.com
GA=13w0d
12.3cm/2.1/10Hz
TIb 1.5
FETUS A
30
15
cm/s
-15
-30
-45
-60
-75
-90


13.05.1987
RAB6-D/OB
MI 0.8
F.YAZICIOGLU www.hafeyaz.com
GA=13w0d
12.3cm/1.4/ 5Hz
TIb 1.4
FETUS A
A DV-S -39.54cm/s
A DV-D -19.30cm/s
A DV-a -7.35cm/s
A DV-TAmax -28.20cm/s
A DV-S/a 5.38
A DV-PI 1.14
A DV-PLI 0.81
A DV-PVIV 1.67
A DV-HR 154bpm
-50
-40
-30
-20
-10
cm/s
10
20
30


13.05.1987
RAB6-D/OB
MI 1.0
F.YAZICIOGLU www.hafeyaz.com
GA=13w0d
10.4cm/1.3/40Hz
TIb 0.6
FETUS A


TOPCUOGLU, HAMIDE
COMP
1.Trim. Card
Har-high
MICRO


FETUS A
1.Trim. Card
Har-high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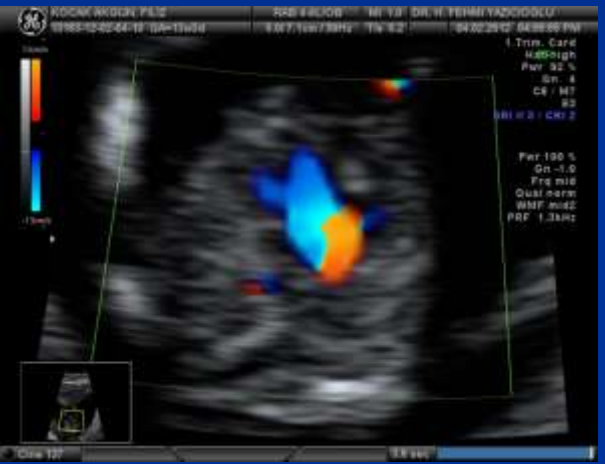
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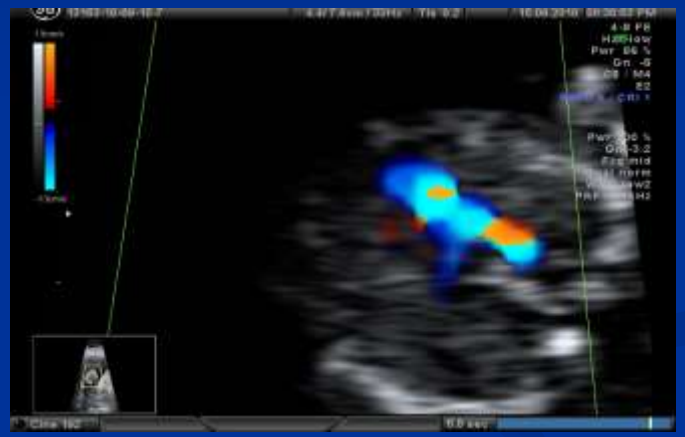
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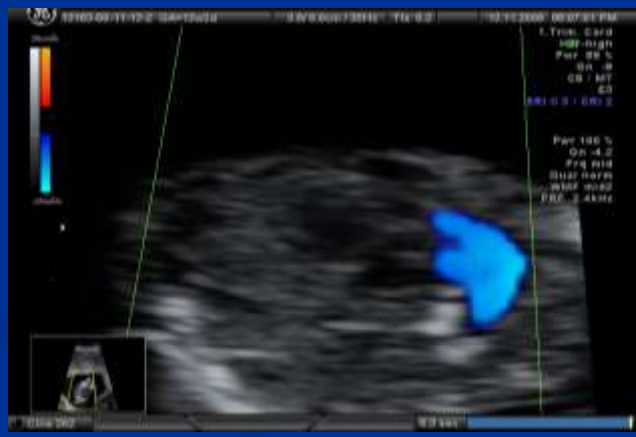
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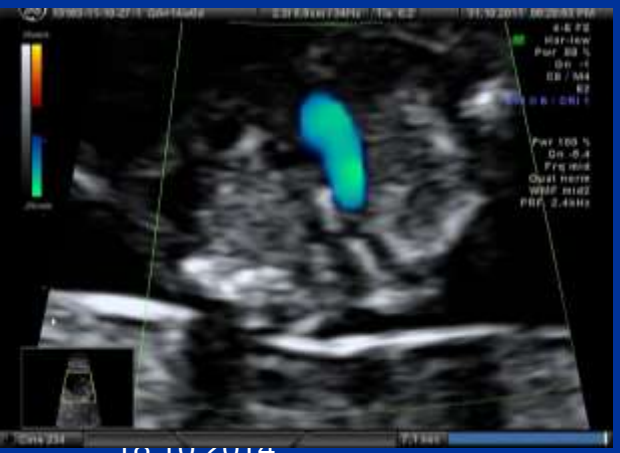
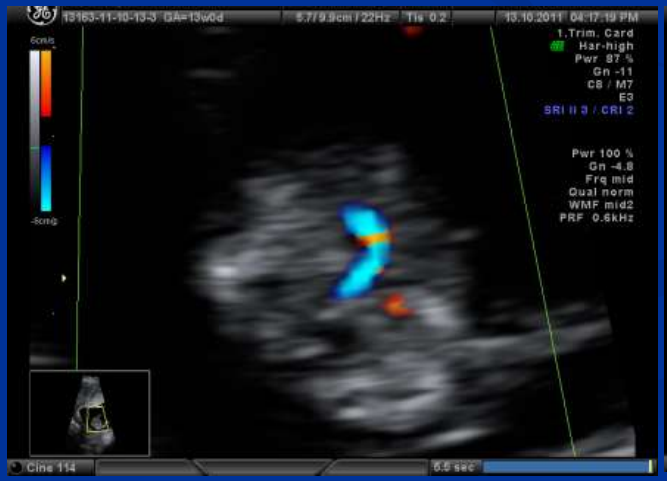
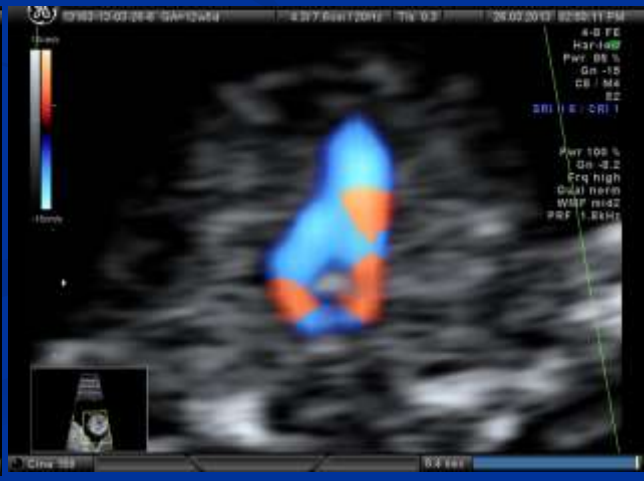
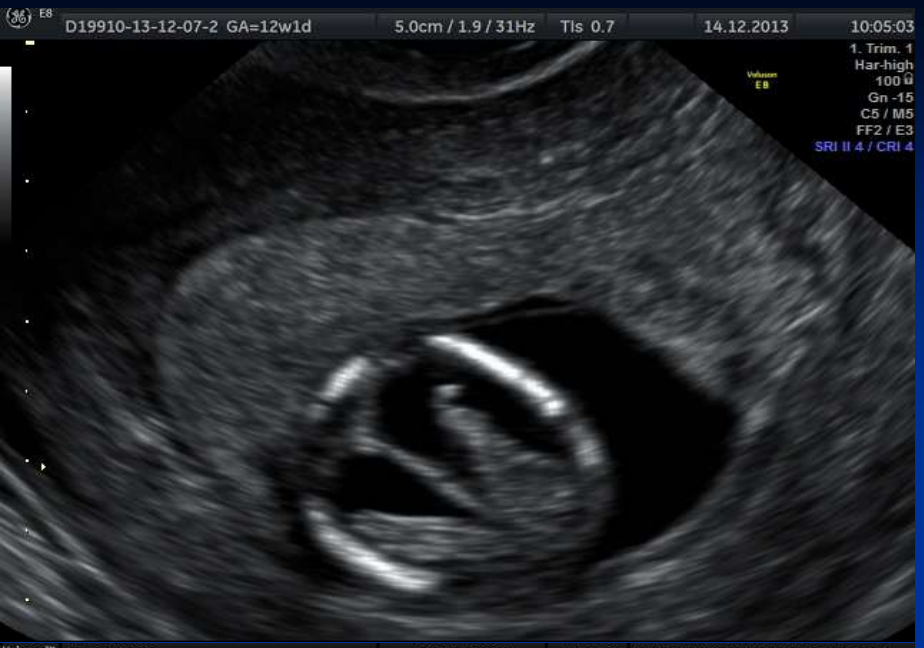
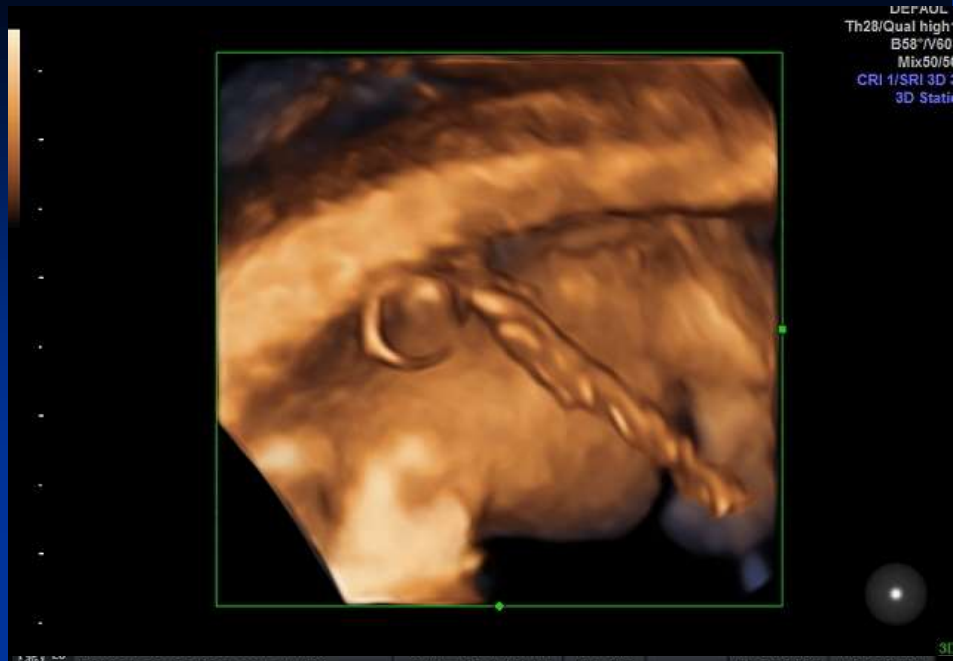



13163-11-10-13-3 GA=13w0d
13.10.2011 04:17:19 PM
1.Trim. Card
Har-high
Pwr 97 %
Gn -11
CB / M7
E3
SRI II 3 / CRI 2
Pwr 100 %
Gn -4.8
Frq mid
Qual norm
WMF mid2
PRF 0.6kHz
Cine 114
6.5 sec




D19910-13-12-07-2 GA=12w1d
5.0cm / 1.9 / 31Hz
TIs 0.7
14.12.2013
10:05:03
1. Trim. 1
Har-high
100
Gn -15
C5 / M5
FF2 / E3
SRI II 4 / CRI 4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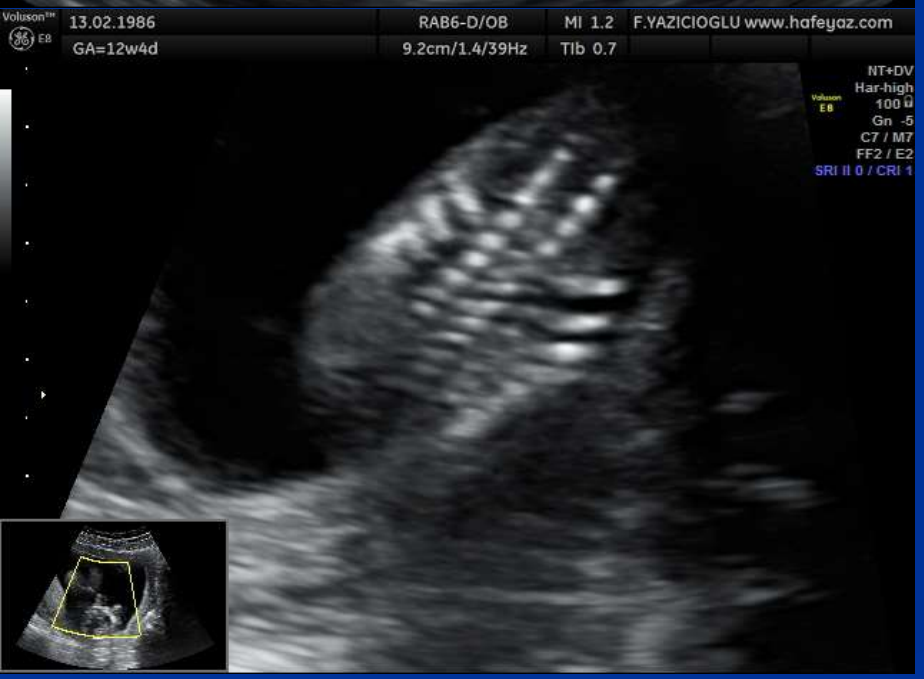
B58°/V60
Mix50/5
CRI 1/SRI 3D
3D Stati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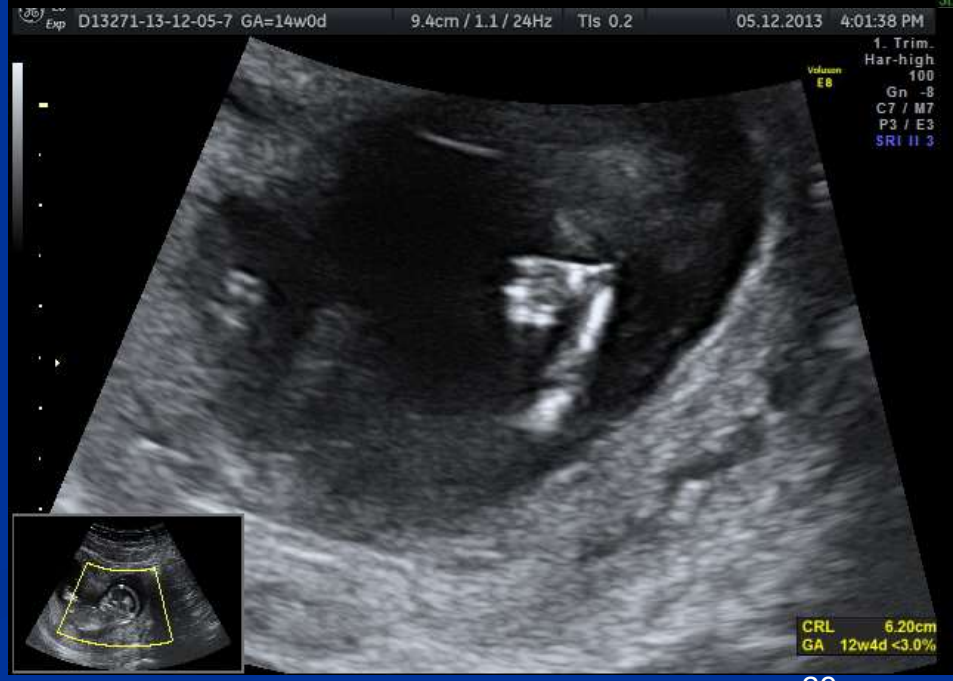
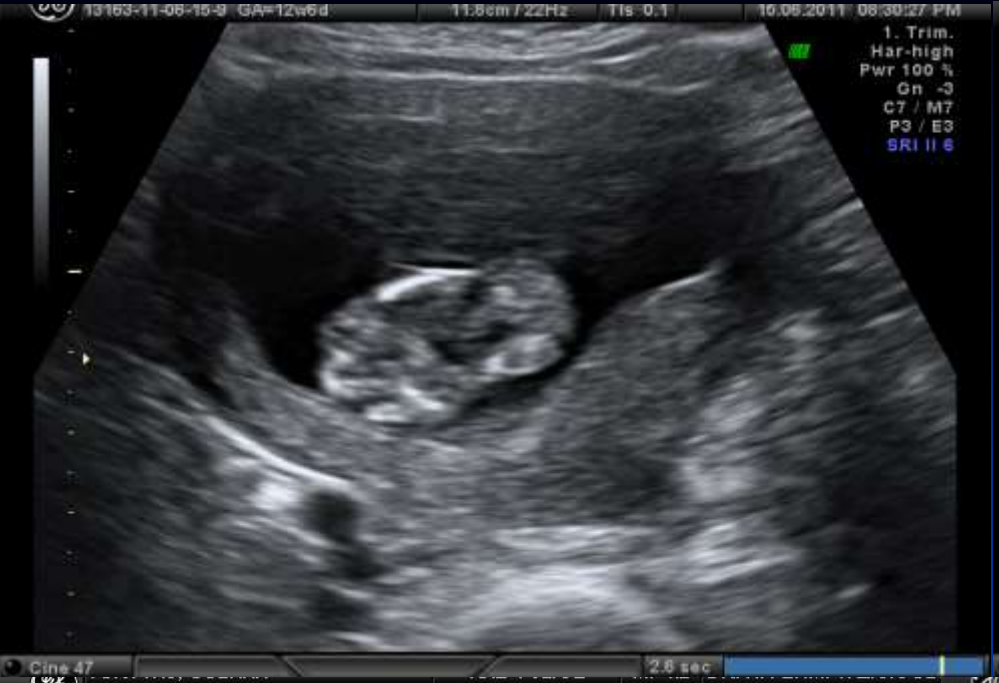
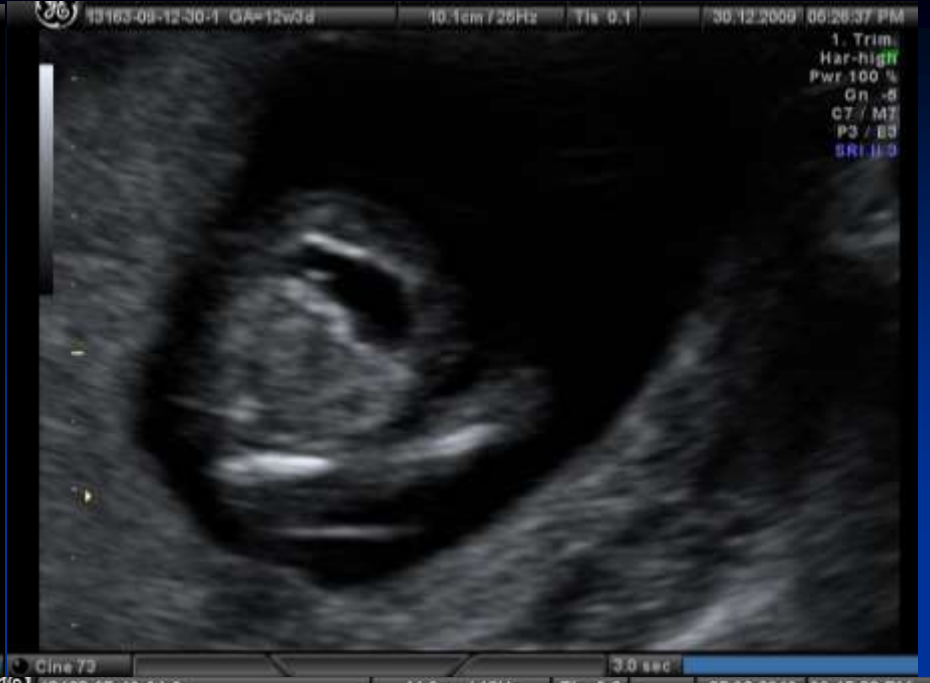
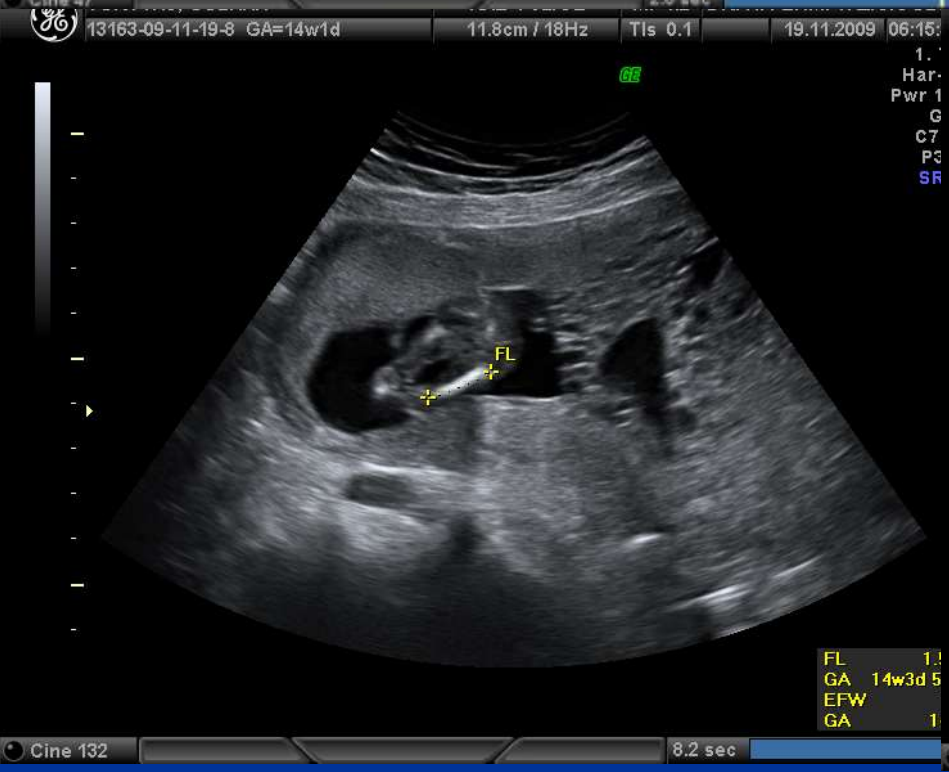
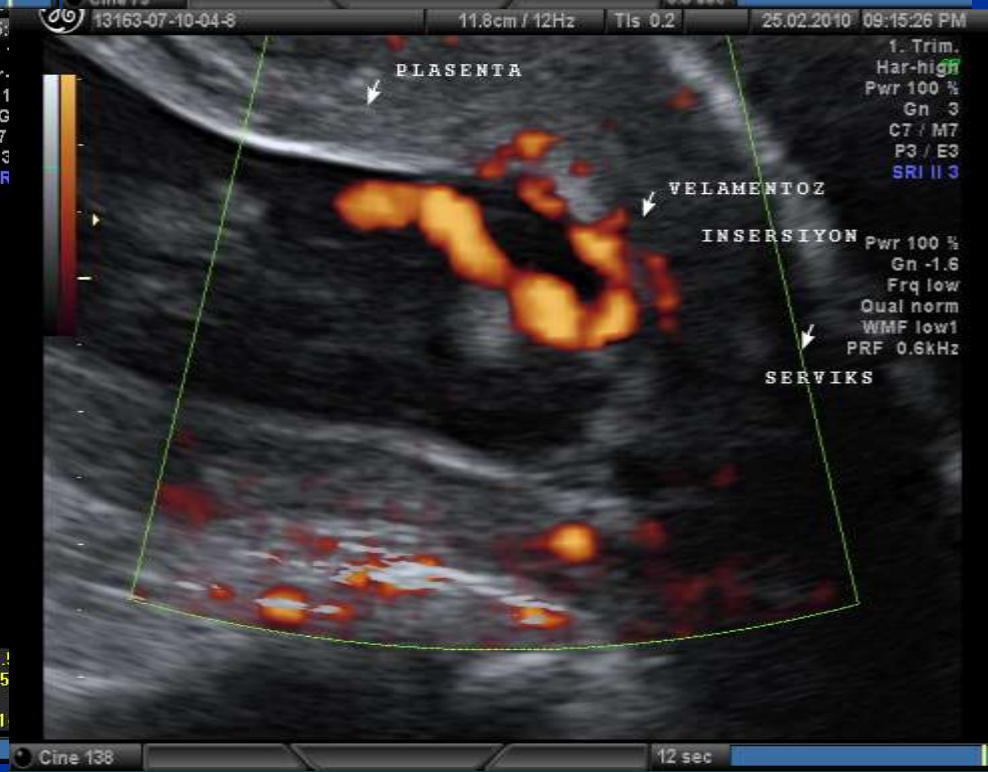
RAB6-D/OB
MI 1.2
F.YAZICIOGLU www.hafeyaz.com
GA=12w4d
9.2cm/1.4/39Hz
TIb 0.7
NT+DV
Har-high
100
Gn -5
C7 / M7
FF2 / E2
SRI II 0 / CRI 1


D13271-13-12-05-7 GA=14w0d
9.4cm / 1.1 / 24Hz
TIs 0.2
05.12.2013
4:01:38 PM
1. Trim.
Har-high
100
Gn -8
C7 / M7
P3 / E3
SRI II 3
CRL 6.20cm
GA 12w4d <3.0%


1. Trim.
Har-high
Pwr 100 %
Gn -3
C7 / M7
P3 / E3
SRI II 6
Cine 47
2.6 sec


1. Trim.
Cine 73
3.0 sec


13163-09-11-19-8 GA=14w1d
11.8cm / 18Hz
Tis 0.1
19.11.2009
FL
FL 1.
GA 14w3d 5
EFW
GA 1
Cine 132
8.2 sec


13163-07-10-04-8
11.8cm / 12Hz
Tis 0.2
25.02.2010 09:15:26 PM
PLASENTA
VELAMENTOZ
INSERSIYON
SERVIKS
1. Trim.
Pwr 100 %
Gn 3
C7 / M7
P3 / E3
SRI II 3
Pwr 100 %
Gn -1.6
Frq low
Qual norm
WMF low1
PRF 0.6kHz
Cine 138
12 sec

11-14 hafta tarama ek avantajları

- Gross anomaliler %50
- Ciddi fetal kalp anomalileri %40-90 elimine edilebilir
- Accreta, vasa previa tanımlanabilir
- Erken ve geç preeklampsi
- Erken ve geç IUGR
- Erken doğum öngörülebilir

Genetik sonogramın avantajları

- NIPT sayısında ciddi azalma
- Ek fetal strüktürel anomalilerin tesbiti
- Atipik kromozomal anomali tanısında artış

ISUOG Önerileri

- Ilk üçay tarama testi sonrası seçilen eşik değere göre:
  - İnvasif test
  - NIPT
  - Takip

ISUOG Önerileri

- NIPT normal bulunan olgularda diğer risk tayin prosedürlerine gerek yoktur
- Anormal veya sınırda kombine risk sonrası invasif teste alternatif olarak NIPT seçeneği sunulabilir
- Çok yüksek riskli(>1:10) ancak ultrasonografik anomali içermeyen olgularda invasif teste alternatif olarak NIPT seçeneği prospektif çalışmalarla değerlendirilmelidir. Güncel uzman görüşü bu olgularda invasif testin yeğlenmesi yönündedir

ISUOG Önerileri

- USG de fetal strüktürel anomali varlığında normal NIPT sonucu olsa bile karyotipleme/array CGH dan vazgeçilmemelidir
- İkizlerde NIPT etkinliği henüz belirsizdir
- NIPT sonucu normal olan gebeye genetik sonogram yapılmamalıdır
- Değişik tarama stratejilerini maliyet ve etkinlik açısından araştıracak Prospektif ve kamu kaynaklarınca desteklenen çalışmalara acilen ihtiyaç vardır

Genetik sonogram n:6286

- Basamaklı Ardışık tarama
- Genetik sonogram
- Duyarlıkta anlamlı bir değişiklik yok (15/17 vs 14/17)
- Yanlış pozitiflikte %32 azalma (390/6269 vs 266/6269)
- Öneri: Ara(intermediate) risk olgularında kullanılabilir bir metod

Shamshirshaz AA et al. J Ultrasound Med 2013; 32:1607-13

Taygetos(Pentadaktylos) Dağı, Sparta, Peleponnes