Contingent screening / NIPT Guidelines

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Recommendation and Citation

Ultraschall in der Medizin
European Journal of Ultrasound

Guidelines & Recommendations

Thieme

DEGUM, ÖGUM, SGUM and FMF Germany Recommendations for the Implementation of First-Trimester Screening, Detailed Ultrasound, Cell-Free DNA Screening and Diagnostic Procedures

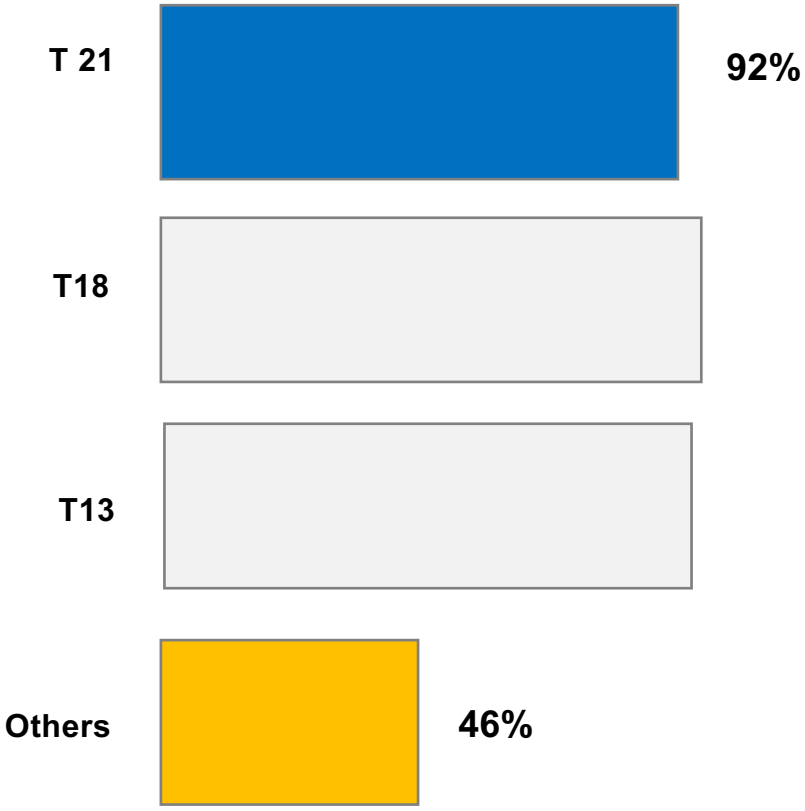
ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice

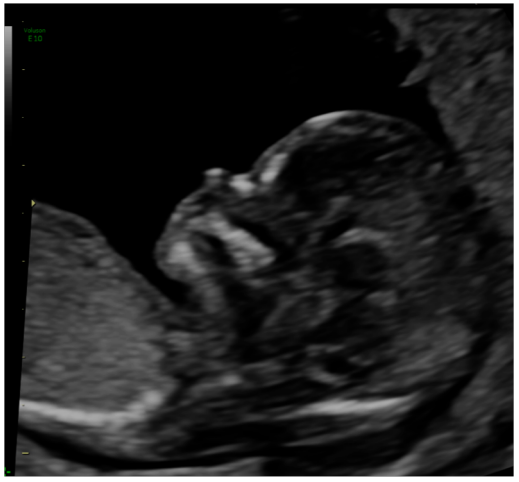
Kozlowski, P., *et al.:* Ultraschall Med.;2018 Jul 12. doi: 10.1055/a-0631-8898.

Ultrasound Obstet Gynecol 2017; 49: 815–816. DOI: 10.1002/uog.17483

Combined Screening

n=108,982; FPR 5.3%





Kagan KO, et al.:Prospective validation of first-trimester combined screening for trisomy 21. Ultrasound Obstet Gynecol. 2009 Jul;34(1):14-8. doi: 10.1002/uog.6412.

Test Performance

aneuploidy	DR %	FPR %	FF %	NR %
Trisomy 21	99.7	0.04	10.7	1.9
Trisomy 18	97.9	0.04	8.6	8.0
Trisomy 13	99.0	0.04	7.0	6.3
Monosomy X	95.8	0.14	10.0	4.1
SCA	100.0	0.04	–	–

DR: detection rate, FPR: false-positive rate, SCA: sex chromosome anomalies except for monosomy X, FF: fetal fraction, NR: non-reportables.

Gil MM, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2017; 50: 302-314

Revello R, et al. Screening for trisomies by cell-free DNA testing of maternal blood: consequences of a failed result. Ultrasound Obstet Gynecol 2016; 47: 698-704

Test Performance – Subgroup Analysis

aneuploidy	pooled data		high-risk population				general population			
	DR %	FPR %	DR %	FPR %	PPV %	NPV %	DR %	FPR %	PPV %	NPV %
Trisomy 21	99.3	0.1	97.3	0.3	91.3	99.9	95.9	0.1	81.6	99.9
Trisomy 18	97.4	0.1	93.0	0.3	84.3	99.9	86.5	0.2	36.6	99.9
Trisomy 13	97.4	0.1	95.0	0.1	87.0	99.7	77.5	0.1	48.8	99.9

DR: detection rate, FPR: false-positive rate, PPV: positive predictive value, NPV: negative predictive value.

Taylor-Phillips S, et al.: Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. BMJ open 2016; 6: e010002

How to calculate?

a priori	Odds	
	Positive	Negative
1:10,000	1 in 10 (10.0%)	1 in 1,250,000
1:1,000	1 in 1.9 (52.6%)	1 in 125,000
1:100	1 in 1.09 (91.7%)	1 in 12,500

Gil MM, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2017; 50: 302-314

Test Failure

Test for	Failure
T21	**0.03 - 11.1%**
T18	**0 - 12.2%**
T13	**0 - 12.2%**
Repeat the Test: Success 60% FF > 4%	

Gil MM, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2017; 50: 302-314

Sex chromosomes

- Turners Syndrome can be diagnosed with ultrasound
- 23% Mosaic
- High Incidence for maternal mosaic
- Screening performance:
  - False positive rate is higher (ca 0.3%)
  - PPV is lower than T21

Gil MM, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2017; 50: 302-314

Sex chromosome aneuploidies and Sex

- 45, X — Monosomy - Turner
- 47, XXX — Triple X
- 47, XXY — Klinefelter
- 47, XYY — Diplo-Y

- Prevalance 1 %
- Fetal sex determination 99%
- 70 % lost to follow-up in studies
- 23% placental mosaics
- PPV 53 %
- Data not provided till 14+0 weeks

- AGS
- Duchenne muscular dystrophy
- Clitoris hypertrophy vs. hypospadias

Kozlowski, et al. Ultraschall Med. 2018 Jul 12. doi: 10.1055/a-0631-8898.

Twin Pregnancies

	cases with trisomy 21				cases without trisomy 21			
author	total	tested as abnormal	%	95 % CI	total	tested as abnormal	%	95 % CI
Lau (2013)	1	1	100	2.5 – 100	11	0	0	0.0 – 28.5
Huang (2014)	9	9	100	66.4 – 100	180	0	0	0.00 – 2.03
Benachi (2015)	2	2	100	15.8 – 100	5	0	0	0.00 – 52.18
Sarno (2016)	8	8	100	63.1 – 100	409	0	0	0.00 – 0.90
Tan (2016)	4	4	100	39.8 – 100	506	0	0	0.00 – 0.73
Pooled analysis			100	95.2 – 100			0	0 – 0.003

- Test failure 5.6%, FF must be stated
- No testing by vanishing twin
- High failure rate in high BMI or after IVF
- No reliable data on Trisomies 18&13

Gil MM, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis.
Ultrasound Obstet Gynecol 2017; 50: 302-314
Bevilacqua E, Nicolaides KH. et al. Performance of screening for aneuploidies by cell-free DNA analysis of maternal blood in twin pregnancies.
Ultrasound Obstet Gynecol 2015; 45: 61-66

Rare aneuploidies

- Prevalance of rare aneuploidies 0.3-0.8%
- No follow up data available
- PPV only 8 %
- American College of Medical Genetics recommends NO Screening
- Triploidies are mostly not detectable

Kozlowski, et al. Ultraschall Med. 2018 Jul 12. doi: 10.1055/a-0631-8898.

Microdeletions & Microduplications

- 1-1.7 % pregnancies with normal findings
- More common than T21 in younger women
- Over 2100 copy number variations
- Independent of maternal age
- Larger microdeletions are offered:
  - DiGeorge Syndrome
  - Prader Willi
  - Cri-du-Chat
    - **Only 11 %**
    - **Theoretical DR 74 %**
    - **Majority false positive**

Do NOT recommend

Kozlowski, et al. Ultraschall Med. 2018 Jul 12. doi: 10.1055/a-0631-8898.

Fetal Blood Group

- DR for rhesus D after 12 weeks 99.7 %
- Determination of Kell, C, c, E, e possible

What is the big question?

Chitty LS, et al. Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. BMJ (Clinical research ed) 2014; 349: g5243

Scheffer PG, et al. Noninvasive fetal blood group genotyping of rhesus D, c, E and of K in alloimmunised pregnant women: evaluation of a 7-year clinical experience. BJOG: an international journal of obstetrics and gynaecology 2011; 118: 1340-1348

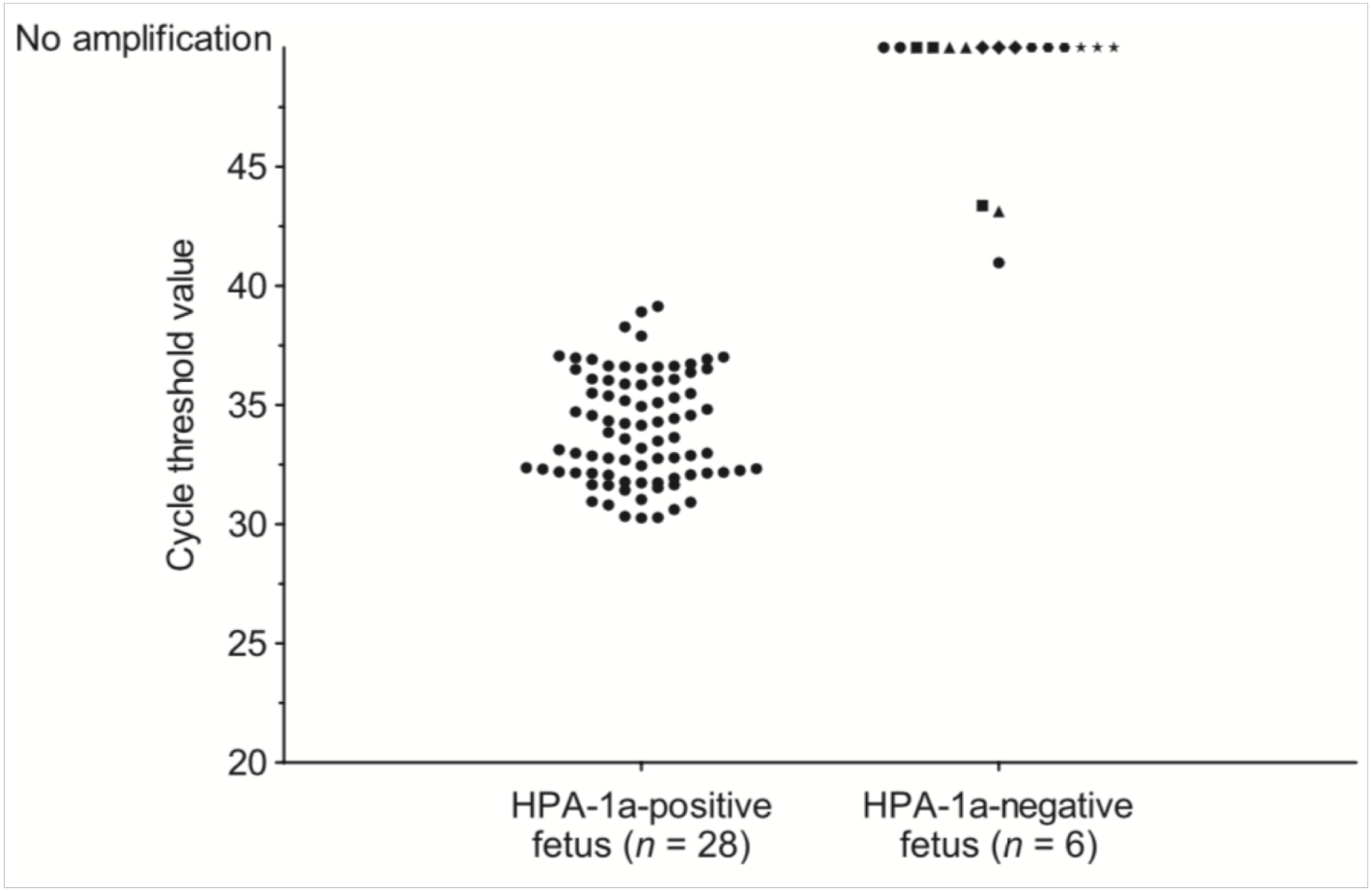
Monogenic Diseases

- Achondroplasia
- Thanatophoric Dysplasia
- Apert Syndrome
- Paternal mutations of cystic fibrosis
- Tuberous Sclerosis
- AR polycystic kidney disease

Chitty LS, et al. Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. BMJ (Clinical research ed) 2014; 349: g5243

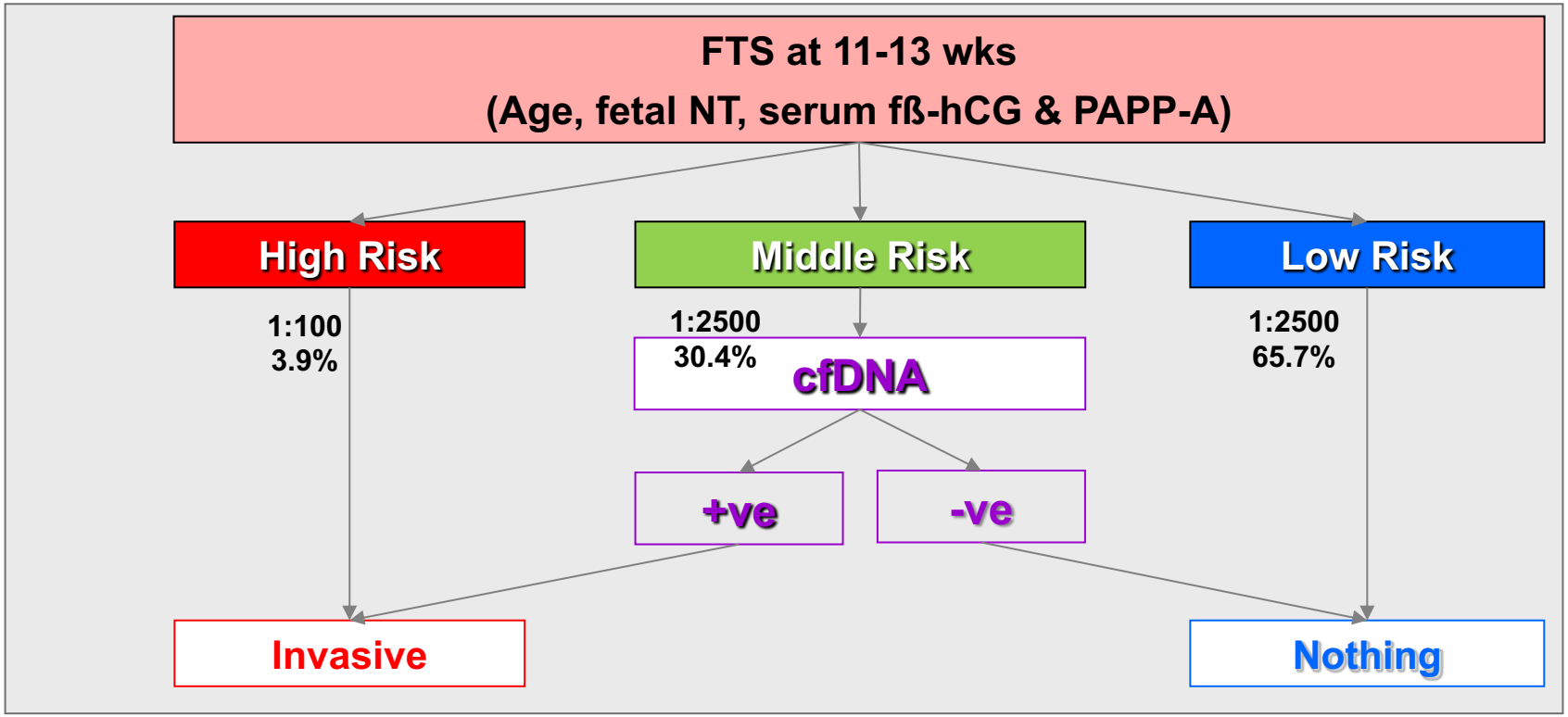
Scheffer PG, et al. Noninvasive fetal blood group genotyping of rhesus D, c, E and of K in alloimmunised pregnant women: evaluation of a 7-year clinical experience. BJOG: an international journal of obstetrics and gynaecology 2011; 118: 1340-1348

Fetal or neonatal alloimmune thrombocytopenia (FNAIT)



Scheffer, et al.: BJOG. 2011 Oct;118(11):1392-5. doi: 10.1111/j.1471-0528.2011.03039.x. Epub 2011 Jul 12.
Noninvasive fetal genotyping of human platelet antigen-1a.
Wienzek-Lischka, et al.: Noninvasive fetal genotyping of human platelet antigen-1a using targeted massively parallel sequencing
15 April 2015 https://doi.org/10.1111/trf.13102

Contingent Screening



Slide: FMF London

43% less CVS; T21 DR %97

Gil MM, Revello R, Poon LC, Akolekar R, Nicolaides KH. Clinical implementation of routine screening for fetal trisomies in the NHS: cell-free DNA test contingent on results from first-trimester combined test. Ultrasound Obstet Gynecol 2015 doi: 10.1002/uog.15783.

Preis-Hypothesis & Cut-off

Risk cut-off	Screen-positive rate (%) Euploid	T21	T18	T13	Invasive testing rate (%)	Cost (€)
1 in 10	0.2	64.9	69.0	58.2	0.9	15 857 000
1 in 20	0.4	71.9	75.1	64.6	1.1	16 147 000
1 in 30	0.6	75.7	78.2	68.1	1.4	16 399 000
1 in 40	0.8	78.1	80.2	70.6	1.6	16 617 000
1 in 50	1.0	79.9	81.7	72.4	1.8	16 811 000
1 in 100	1.8	84.7	85.7	77.7	2.6	17 645 000
1 in 500	5.4	91.9	91.6	87.1	6.3	21 323 000
1 in 1000	8.7	93.9	93.2	89.9	9.5	24 519 000
1 in 1500	11.5	94.9	94.1	91.4	12.4	27 379 000
1 in 2000	14.2	95.6	94.7	92.4	15.1	30 071 000
1 in 2500	16.8	96.1	95.2	93.2	17.6	32 600 000
1 in 3000	19.2	96.5	95.7	93.8	20.0	35 008 000

Patients with a risk above the upper risk cut-off were classified as screen positive. Costs refer to a population of 100 000 pregnancies including 701 with trisomy 21, 216 with trisomy 18 and 108 with trisomy 13.

- Only FTS: mat. Age, NT, DV PI
- 1:100 cut-off
- 2645 invasive Diagnostics
- 150 Euro Screening
- 1000 Euro CVS
- **17,645,000 Euro** in Total

- Only cfDNA-Test
- 1,4% CVS
- 500 Euro
- 1000 Euro CVS
- **51,428,000 Euro** in Total

First-trimester contingent screening for trisomies 21, 18 and 13 by fetal nuchal translucency and ductus venosus flow and maternal blood cell-free DNA testing
Kagan KO et al., Ultrasound Obstet Gynecol 2015; 45; 42-47

Preis-Hypothesis & Cut-off

	Upper risk cut-off					
Lower risk cut-off	*1 in 10*	*1 in 20*	*1 in 30*	*1 in 40*	*1 in 50*	*1 in 100*
1 in 500						
FPR	0.37	0.59	0.80	0.99	1.16	1.92
DR for T21	91.6	91.7	91.7	91.7	91.8	91.8
DR for T18	90.9	91.1	91.2	91.2	91.3	91.4
DR for T13	84.9	85.4	85.6	85.8	86.0	86.4
1 in 1000						
FPR	0.48	0.70	0.91	1.10	1.27	2.03
DR for T21	93.6	93.7	93.7	93.7	93.7	93.8
DR for T18	92.4	92.6	92.7	92.8	92.8	93.0
DR for T13	87.4	87.9	88.2	88.4	88.5	88.9
1 in 1500						
FPR	0.58	0.80	1.00	1.19	1.37	2.13
DR for T21	94.6	94.7	94.7	94.7	94.7	94.8
DR for T18	93.3	93.5	93.6	93.6	93.7	93.8
DR for T13	88.8	89.3	89.6	89.8	89.9	90.3
1 in 2000						
FPR	0.67	0.89	1.10	1.29	1.46	2.22
DR for T21	95.3	95.3	95.4	95.4	95.4	95.5
DR for T18	94.0	94.1	94.2	94.3	94.3	94.5
DR for T13	89.8	90.3	90.6	90.7	90.9	91.3
1 in 2500						
FPR	0.76	0.98	1.18	1.37	1.55	2.31
DR for T21	95.8	95.8	95.9	95.9	95.9	96.0
DR for T18	94.4	94.6	94.7	94.8	94.8	95.0
DR for T13	90.5	91.0	91.3	91.5	91.6	92.0
1 in 3000						
FPR	0.85	1.06	1.27	1.46	1.63	2.39
DR for T21	96.3	96.2	96.3	96.3	96.3	96.3
DR for T18	94.9	95.0	95.1	95.2	95.2	95.3
DR for T13	90.7	91.6	91.9	92.1	92.2	92.6

- Contingent-Screening
- 150 Euro US-Control
- 500 Euro cfDNA-Test
- 1,82% CVS
- 1000 Euro CVS
- 25,818,500 Euro Total

First-trimester contingent screening for trisomies 21, 18 and 13 by fetal nuchal translucency and ductus venosus flow and maternal blood cell-free DNA testing
Kagan KO et al., Ultrasound Obstet Gynecol 2015; 45; 42-47

Diagnostics

- Conventional microscopic karyotyping (G-band technique with a resolution of 7 – 10 million bases)
- Fluorescence in situ hybridization (FISH)
- Quantitative real-time polymerase chain reaction (qPCR)
- Molecular genetic examination of the submicroscopic structure of the chromosomes via comparative genomic hybridization (array-CGH with a significantly higher resolution of 25 000 – 100 000 bases)
- Individual gene analyses

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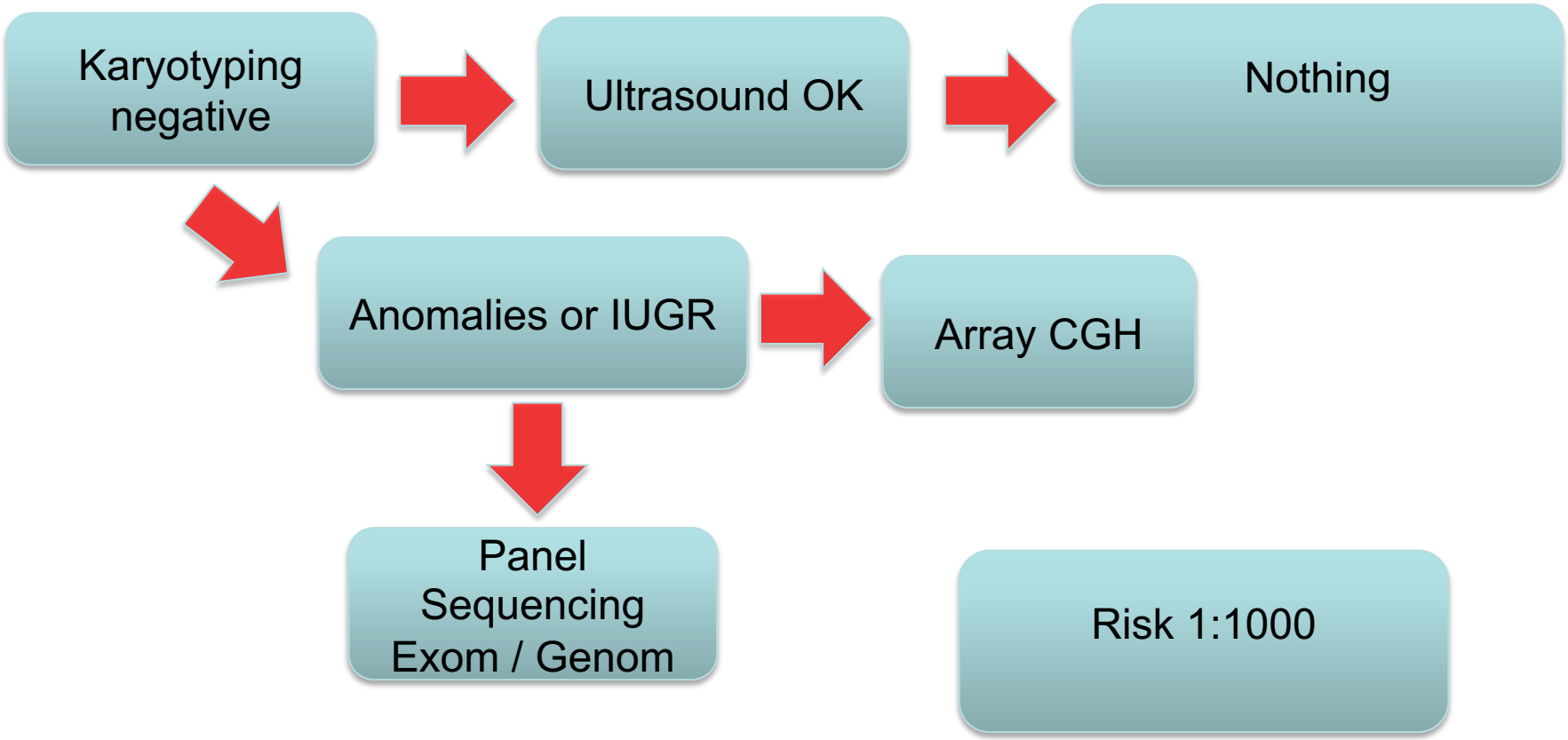
Diagnostics



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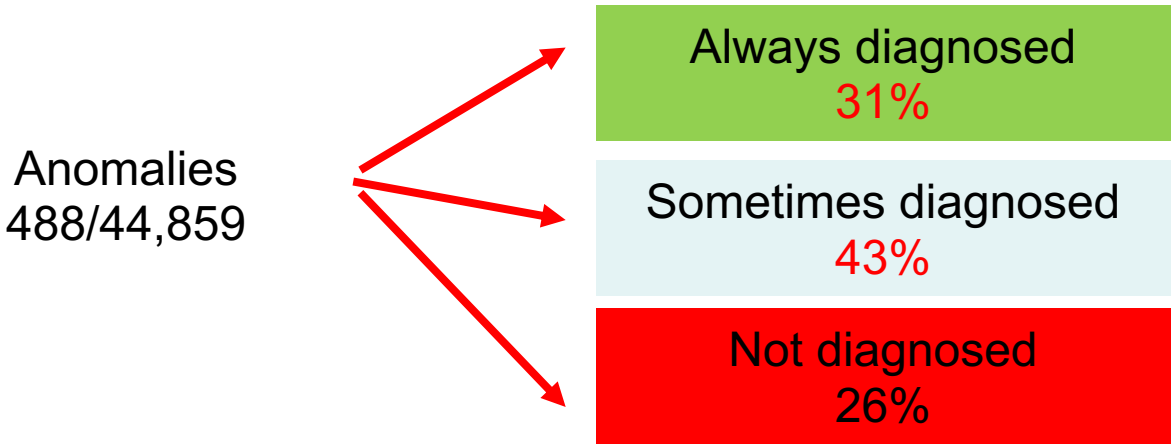
Screening at 1. Trimester



Syngelaki, *et al.*, 2011

Screening

Always diagnosed
31%

Acrania

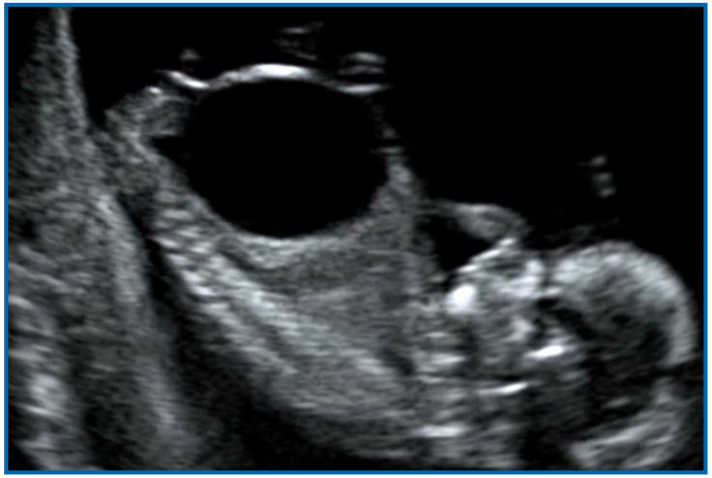
Holoprosencephaly

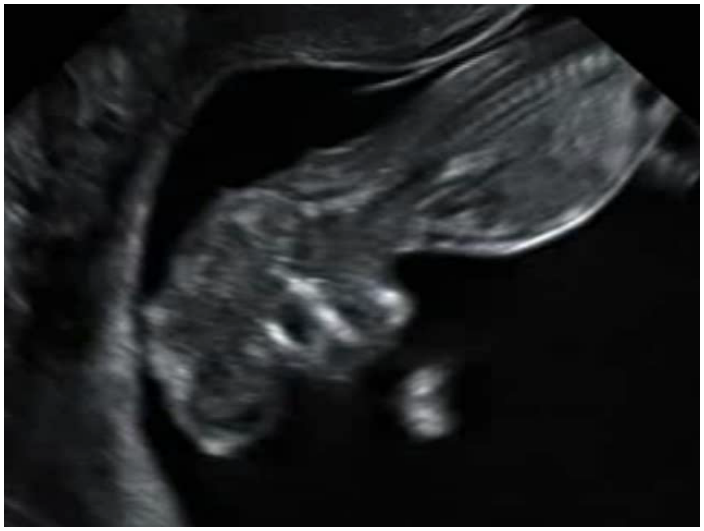
Exomphalos

Gastroschisis

Megacystis

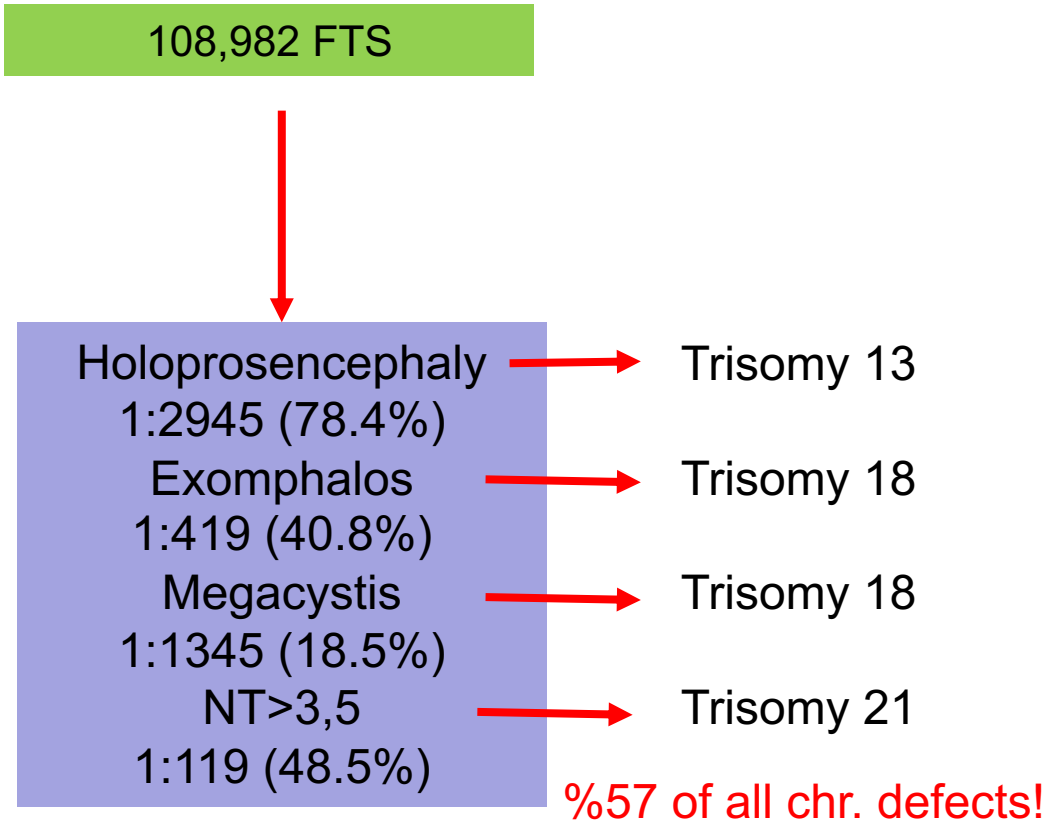
Body stalk anomaly





Syngelaki, *et al.*, 2011

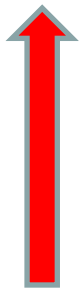
Screening at 1. Trimester



Syngelaki, *et al.*, 2016

Statistics in Germany

Merkmale	2010	2011	2012	2013	2014	2015	2016	2017
Insgesamt	110 431	108 867	106 815	102 802	99 715	99 237	98 721	101 209
Rechtliche Begründung								
Medizinische Indikation	3 077	3 485	3 326	3 703	3 594	3 879	3 785	3 911
Kriminologische Indikation	24	25	27	20	41	20	28	20
Beratungsregelung	107 330	105 357	103 462	99 079	96 080	95 338	94 908	97 278
unter 12	107 852	105 976	104 069	100 002	96 935	96 442	95 892	98 496
12 bis 21	2 117	2 411	2 299	2 238	2 196	2 161	2 199	2 059
22 und mehr	462	480	447	562	584	634	630	654

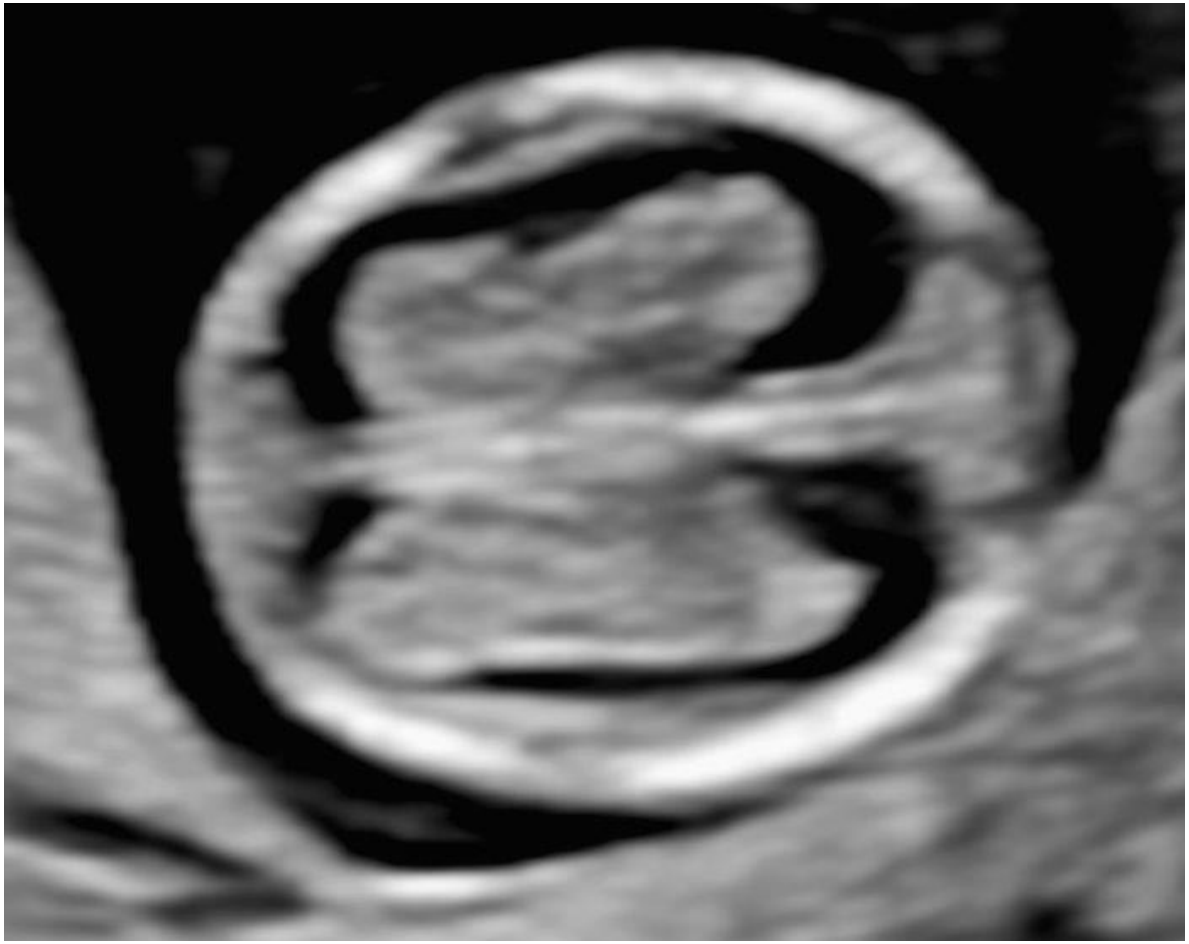


ca. %30

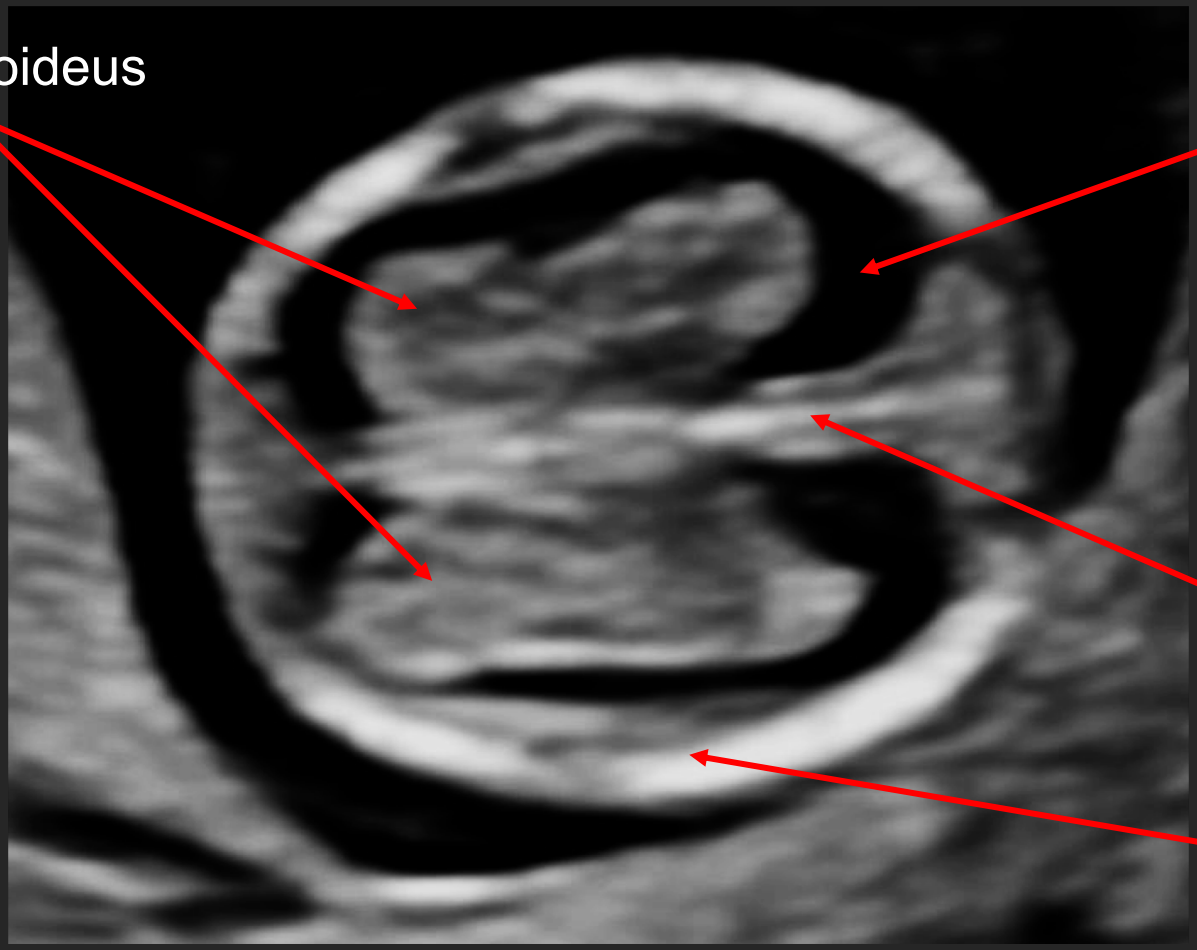
cfDNA-Test

DESTATIS
Statistisches Bundesamt

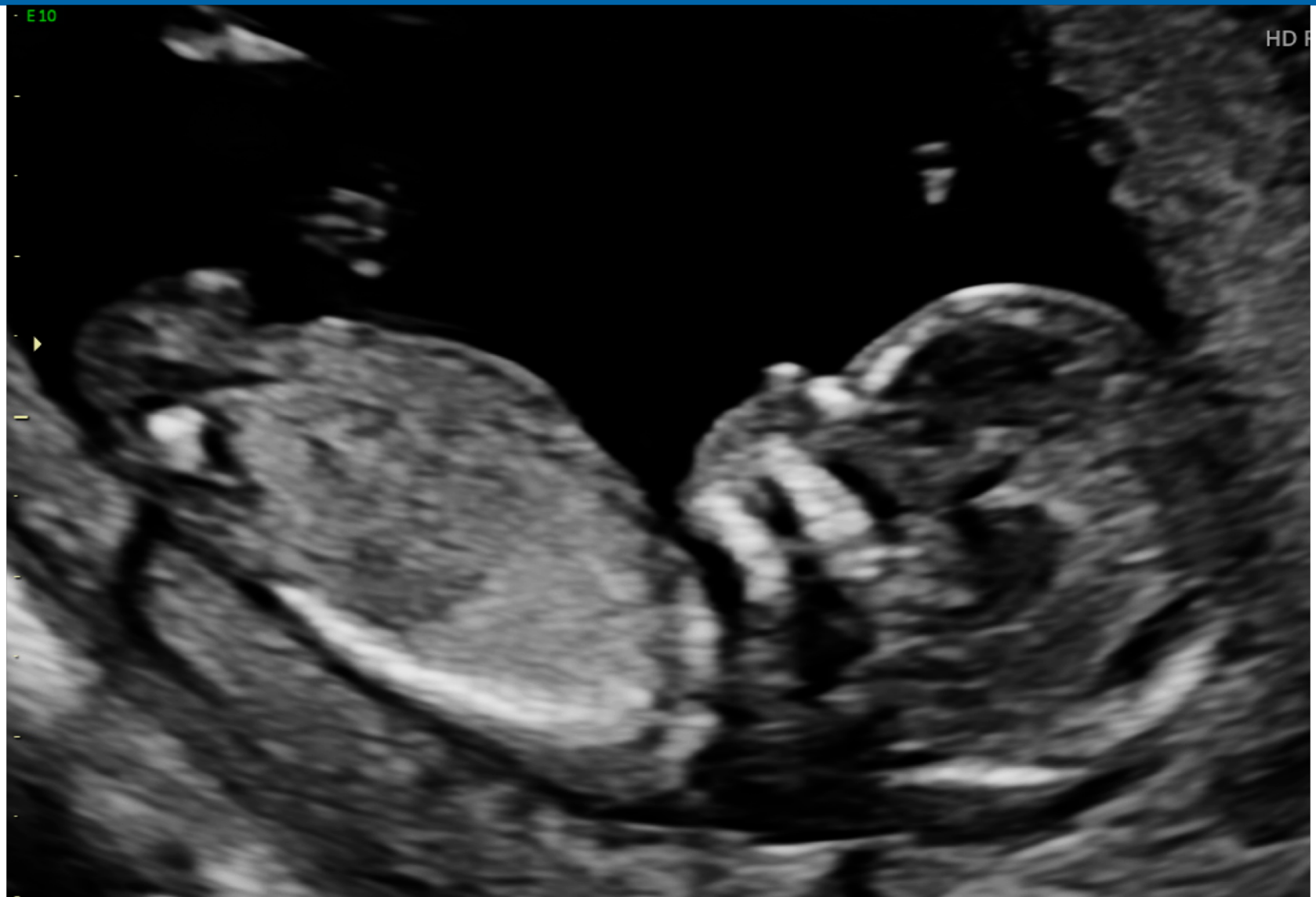
BPD



BPD



NT & CRL



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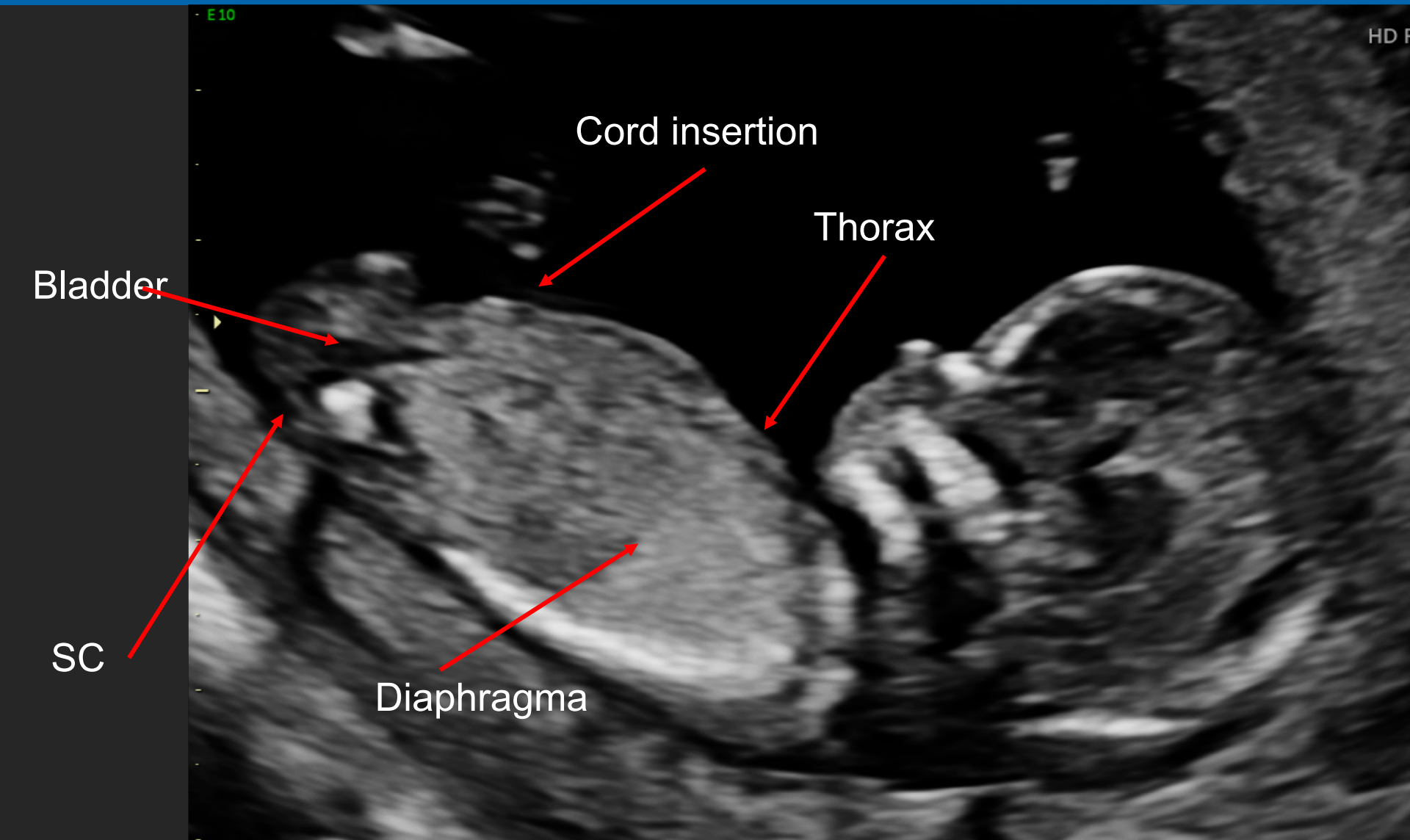

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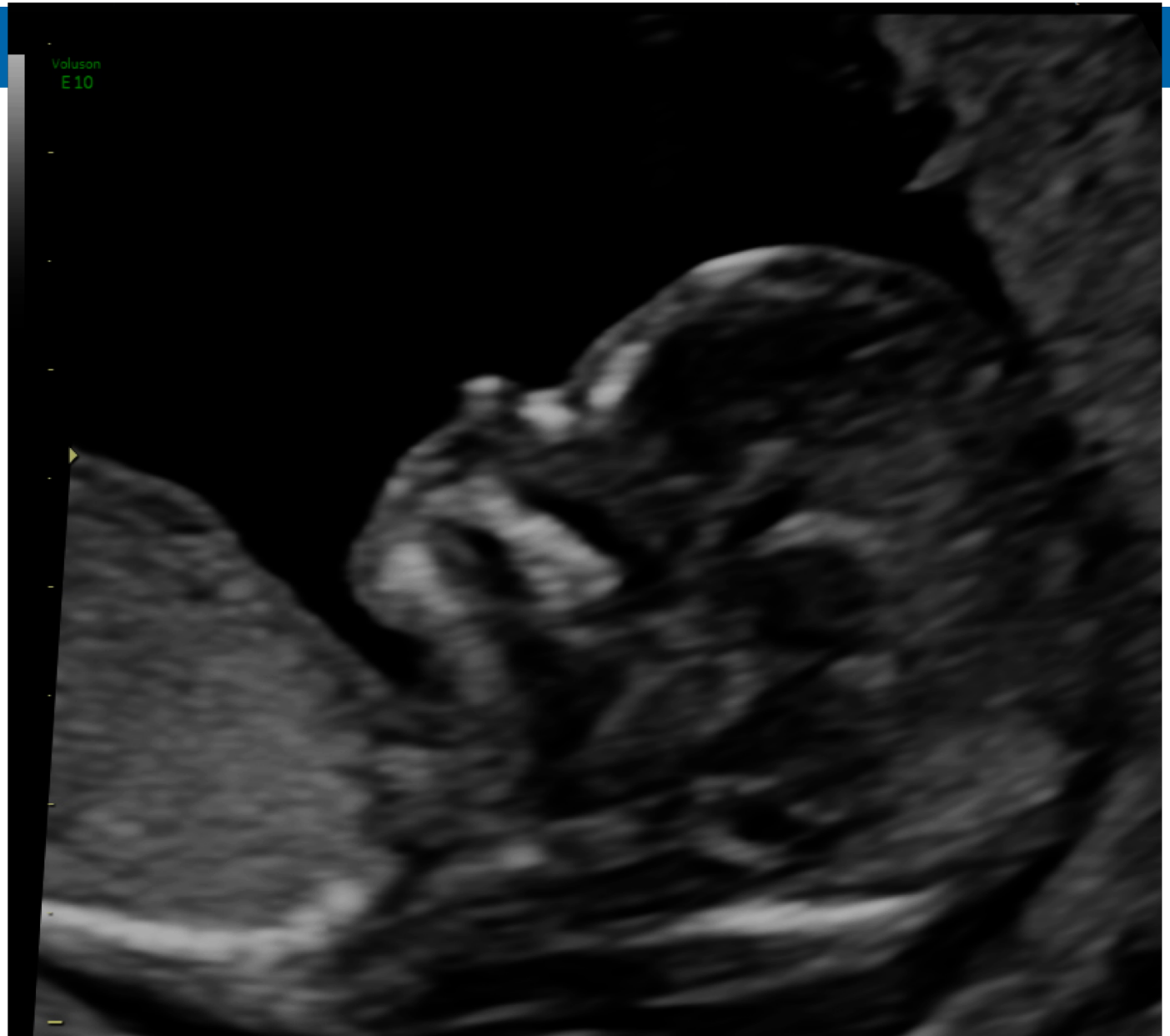
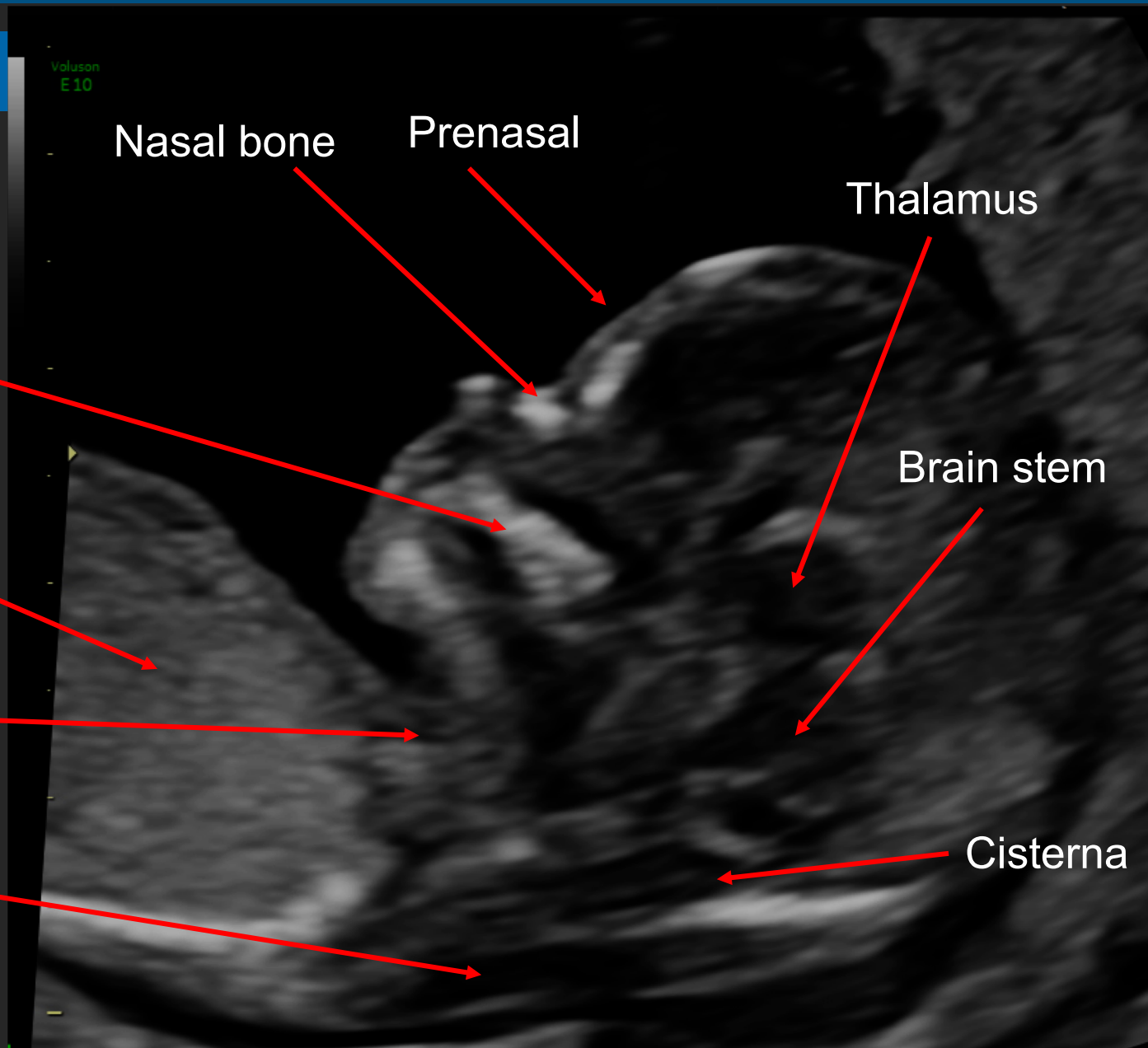
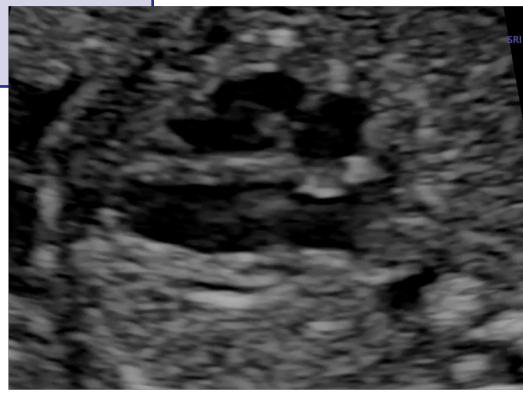


NT & CRL


Voluson
E 10
Nasal bone
Prenasal
Thalamus
Maxilla
Brain stem
Diaphragma
Trachea
Cisterna
Nuchal trans.

Fetal Heart

Method	Detection Rate
History	**10 %**
NT/DV/TR	**58 %**
4CV/NT/DV/TR	**75 %**



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Thank you.