First Trimester Fetal Genetic Analysis: It's Not All About Down's Syndrome

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Disclosures

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Relevant Financial Relationships:
Received small honoraria from the following companies for giving scientific lectures:
Ariosa Diagnostics; Illumina, Inc.; Sequenom, Inc.
These lectures did not endorse the companies or their products and focused completely on the science.

Learning Objectives

After completing this presentation, the learner will be able to:

1: Understand the screening approaches to fetal aneuploidy and other fetal genetic disorders

2: Understand the information available through diagnostic testing by CVS in the first trimester

3: Improve the ability to counsel patients on genetic screening and diagnostic approaches.

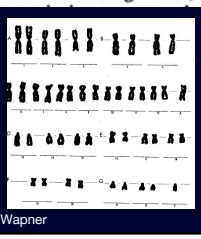
Lecture Outline

- Principals of Screening
- Characteristics of an Ideal Prenatal Screening Test
- Screening For Down Syndrome
- Calculation of Likelihood Ratio
- Prospective Study Outcomes - Combining Mat age, NT, and Biochemistry
- Cell free fetal DNA in the Maternal Circulation
- Meta-Analysis of NIPT Performance 2016
- Cell free DNA in Low Risk Patients
- Cell free fetal DNA: Clinical Challenges
- Value of NT and Biochemical Screening Beyond Common Aneuploidy
- Value of NT and Biochemical Screening Beyond Common Aneuploidy
- Early Diagnosis of Structural Anomalies with Ultrasound
- Invasive Testing Methods - What is the Risk?

THE LANCET, JUNE 18, 1977

WHO'S FOR AMNIOCENTESIS?

Virtually all chromosomal aberrations and many biochemical disorders can be detected by amniocentesis and prenatal diagnosis. Although errors do occur in cytogenetic and biochemical investigations,[1,2] there is a strong case for prenatal



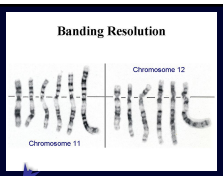
Screen ing for Down Syndrome

Maternal Age

Cut-Off	Liveborn Risk of Down Syndrome	Second Trimester Risk of Down Syndrome
Age 35	1:380	1:270

"...the age limit is arbitrarily decided by logistical concerns and is not the consequence of a sudden biologic difference between women above and below any given risk".

NICHD, 1979



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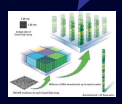

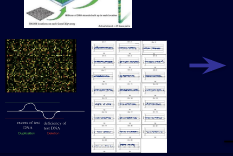

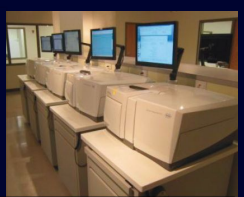

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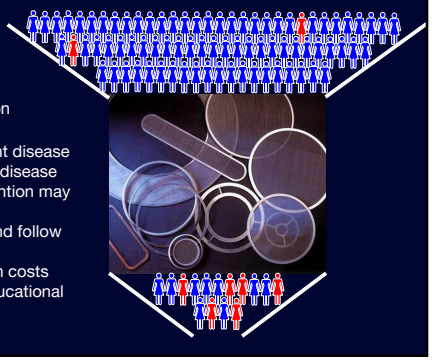
Principals of Screening

Identify a high risk group who may need to consider further testing



- Healthy population
- Reliable
- Relatively frequent disease
- Impairing or fatal disease
- Beneficial intervention may be possible
- Prompt testing and follow up
- Benefits outweigh costs
- Voluntary and educational

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Characteristics of an Ideal Prenatal Screening Test

- **High sensitivity - Identifies a high percentage of affected individuals**
- **High specificity - Does not alarm a high percentage of unaffected individuals**
- **Positive early enough in gestation to allow maximal options and safety**
- **Easy and inexpensive to perform**

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Screening For Down's Syndrome

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Maternal Age is a Screening Test

Age @ Delivery	DS Risk	Total CA Risk
20	1/166	1/526
25	7	1/476 (1/4
30	1/125	1/385 %)
31	0	1/385
32	1/950	1/322
33	1/909	1/286
34	1/769	1/238
35	1/602	1/192 (1/2
36	1/485	1/156 %)
37	1/378	1/127
38	1/289	1/102
39	1/224	1/83

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Maternal Age Screening for Down Syndrome

"…the age limit is arbitrarily decided by logistical concerns and is not the consequence of a sudden biologic difference between women above and below any given risk".

NICHD, 1979

Maternal Age ≥35

Risk Cutoff: (Second Trimester) 1:270
Population at Risk (FPR) 14.2%
Detection Rate 50%
Detection Rate for 5% FPR 30%
Odds of Being Affected 1:100

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Down Syndrome screening has moved from the second to the first trimester

More Accurate
Safer
Patients Prefer

Performing invasive testing for maternal age alone can no longer be justified

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First Trimester Biochemical Screening
Down Syndrome Cases

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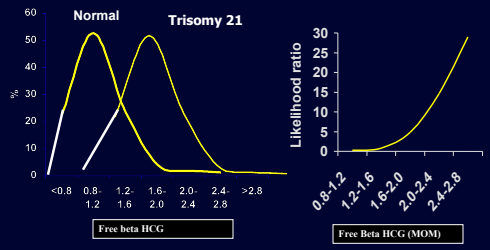
Calculation of Likelihood Ratio



A priori age risk 1 in 200
Likelihood ratio = 0.5 Adjusted risk 0.5 in 200 or ~ 1 in 400
Likelihood ratio = 2.0 Adjusted risk 2.0 in 200 or ~ 1 in 100

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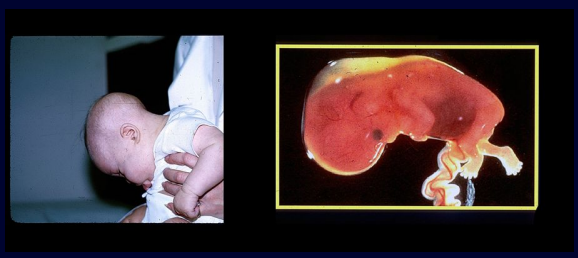
Nuchal Translucency



"the skin is deficient in elasticity… too large for the body"
Langdon Down

Observations on an Ethnic Classification of Idiots.
Clinical Lecture Reports, London Hospital 1866;3;259.

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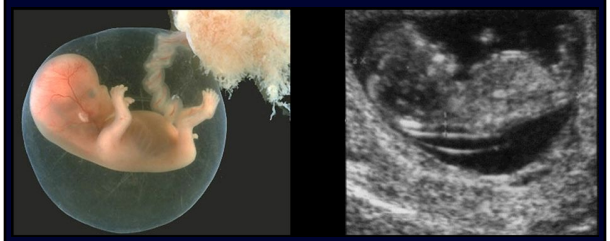
Nuchal Translucency at 11-14 weeks



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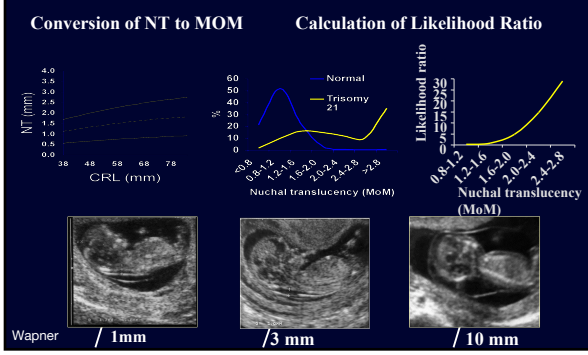
Steps In Conversion Of NT To Down Syndrome Risk



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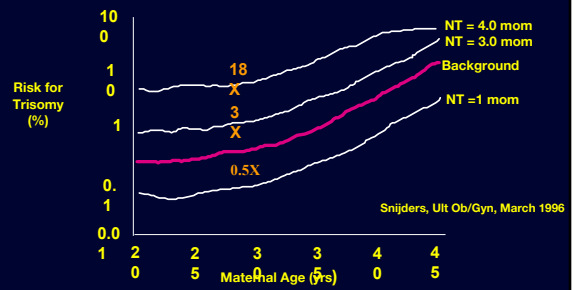
First Trimester Screening for Trisomy 21 Nuchal Translucency



Down Syndrome Risk = Age Risk X NT Likelihood Ratio

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Combined First Trimester Screening for Trisomy 21

Re-evaluation of Risk Based on Multiple Markers

Variable	Result	Ratio
Maternal age	30 years old	1:525
Modifier	**Result**	**LR**
NT (mm)	2.0 MOM	2.2
Biochemical risk: HCG + PAPP A	HCG - 1.8 MOM PAPP A - .6 MOM	2.9

Final Risk (1:525 x 2.2 x 2.9)

1:82

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Prospective Study Outcomes Combining Mat age, NT, and Biochemistry

First Trimester DR at 5% SPR (1:270)

Study	Patients	Down Cases	Detection Rate
BUN	8,216	48/61	79%
FaSTER	33,557	100/117	86%
SURUSS	47,053	84/101	83%
Nicolaides	75,821	301/325	93%
TOTAL	167,210	533/604	88%

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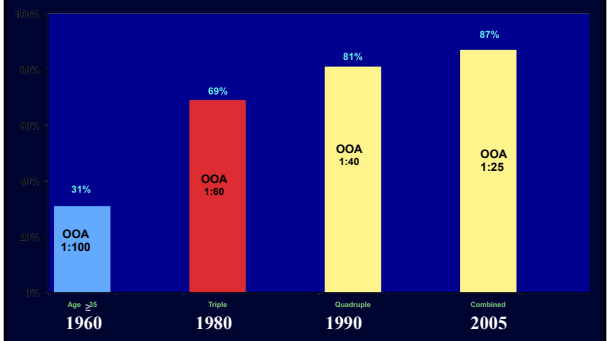
Down Syndrome ScreeningApproach: Observed Detection Rates for 5% FPR



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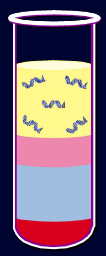
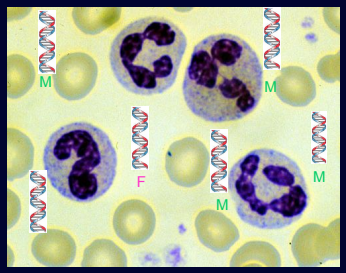
Combined: PAPP-A, free β HCG, NT

All screens include maternal age

Evolving Appreciation of the Top Layer of the Gradient





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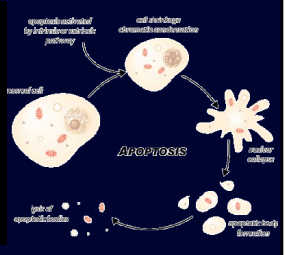
Cell free fetal DNA in the Maternal Circulation

Where does Cell Free DNA come from?

- Circulating cells go through a life cycle, which ends in programmed cellular death called **apoptosis**
  - As a result of apoptosis, DNA gets cleaved into small fragments 150 to 200 base pairs long
- DNA molecules that are released into the blood from dead or apoptotic cells are no longer part of intact cells and are called 'cell free DNA'
- During pregnancy, maternal blood contains a mixture of **both** maternal and fetal cell free DNA



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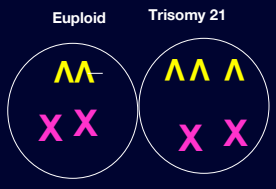
Relative Chromosome Dosage (RCD)



Ratio Chromosome 21:1

In Placenta:

Euploid	Trisomy 21
1:1	3:2

In Maternal Circulation

10% Fetal DNA/90%MaternalDNA

Euploid	Trisomy 21
1:1	1.05:1

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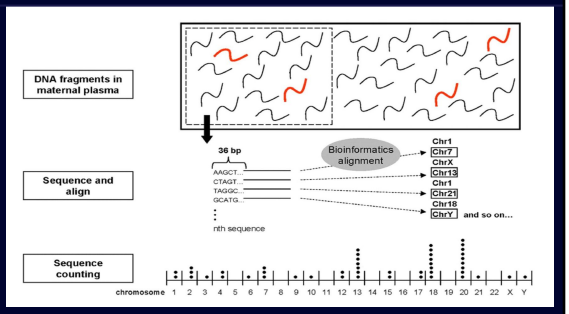
Mass Parallel (Shotgun)Sequencing Analysis of Fetal DNA



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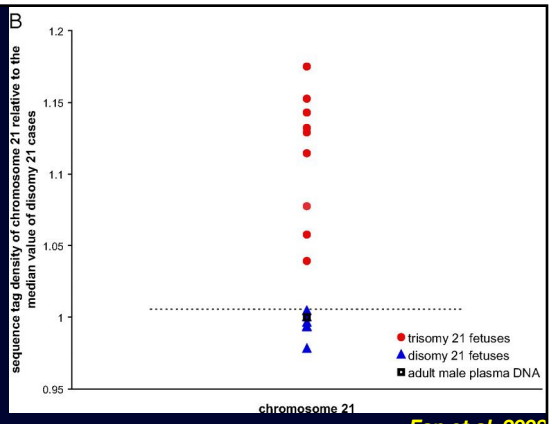
Zhong, X, Holzgreve, W, *Glob. libr. women's med 2009*



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Fan et al, 2008

Meta Analysis of NIPT Performance 2016

High RIsk		Sens	FPR	PPV
High Risk				
	Trisomy 21	91	0.3	91
	Trisomy 18	84	0.3	84
	Trisomy 13	87	0.1	87
Low Risk	**Trisomy21**	**95.9**	**0.1**	**82**
	Trisomy18	86.5	0.2	37
	Trisomy 13	77.5	0.1	49

Trisomy	Sens	FPR
Sex Chrom	86%	0.6%

No difference by MPSS (24), targeted sequencing(9) or SNP (5)

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Taylor Phillips et al: BMJ Open 20

cfDNA in Low Risk Patients

	Maternal Age <35 (DS 1:630)	FTS <1/270 (DS 1:1870)
Total	11,994	14,957
Sensitivity	100%	100%
Specificity	99.95%	99.95%
PPV	76.0%	50.0%
NPV	100%	100%
LR+	1996	1869
LR-	0	0

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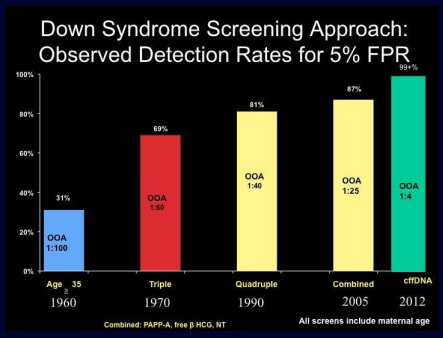
cffDNA
An Excellent Screening Test



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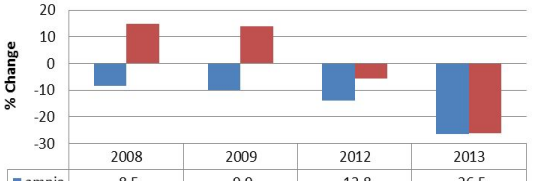
Yearly Change in Volume of Prenatal Diagnostic Procedures 2008-2013



	2008	2009	2012	2013
amnio	-8.5	-9.9	-13.8	-26.5
cvs	14.9	13.8	-5.5	-26

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cffDNA: Clinical Challenges

- No call tests: 3-5%
  - Failure to extract adequate material
  - Individual variation in amount of cffDNA
- False Negative Results

Fetal Fraction	Expected ratio for Trisomy
4%	1.02
10%	1.05
20%	1.10
40%	1.20

Low fetal fraction associated with maternal BMI
20% at >250 lbs
50% at >350 lbs
It is not known if repeating test will provide a result

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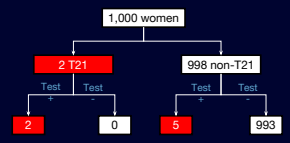
cffDNA: Clinical Challenges

False positives

T21 prevalence: 1 in 500
99% detection 0.5% false positive



	# of false positives at different FPR			
	5%	1%	0.5%	0.1%

For 5000 Delivery Service

Contamination
Unrecognized or vanishing twin
Confined Placental mosaicism
Low level maternal mosaicism

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Value of NT and Biochemical Screening Beyond Common Aneuploidy

- **Chromosome Abnormalities Other than Common Trisomies**
- **Early Identification of Structural Abnormalities**
  - **•Congenital Heart Disease**
  - **•Other Anomalies**
- **Mendelian Genetic Disorders**
- **Poor Pregnancy Outcome**
  - **•Placental Function**
  - **•Obstetrical Disorders**

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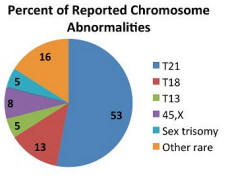
Advanced Maternal Age: Residual Risk for a Cytogenetic Abnormality after cffDNA



	Freq of Chrom Abn	% Trisomy 21,18,13
< 35	0.93%	18%
35	Maternal Age	37%
40	2.1%	68%
45	6.6%	78%

Amniocentesis Performed for AMA

Ferguson-Smith, M.A. Prenatal Diag 1984

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

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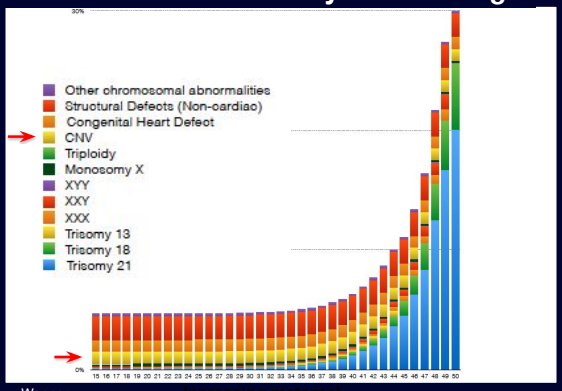
Rate Of Abnormalities By Maternal Age



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Increasing maternal

Positive First Trimester Screen
Residual Risk for a Karyotype Abnormality after NIPT

State of California Screening Program
N= 1,324,607 Screened
Screen Positive
68,990 (5.2%)

Invasive Testing
26,059 (37.7%)

Abnormal
2992 (11.5%)

Detectable by NIPT
2499 (74.9%)
(Includes Sex Chr 247 (8.2%))

Not Detectable by NIPT
504 (16.8%)

Mosaic	186	(6.2%)
Other Tris	92	(3.1%)
Ins/Del	88	(2.9%)
Structural	101	(3.3%)
Balan	97	(3.2%)
Unbal	3	(0.1%)
Triploid	29	(1.0%)
Marker	9	(0.3%)

For Patients with Positive First Tri Screen
Residual Risk of Chromosome Abnormal after Normal NIPT
1:52

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Norton: SMFM

Detection Rate and FPR for ALL Chromosome Abnormalities Sequential Screen vs cfDNA

N= 452,901
N = 2575 Chromosomal Abnormality (1:176)

California Prenatal Screening Program with mandated reporting of all chromosome abnormalities diagnosed prenatally or at age ≤1 y

	Detection Rate	FPR
cfDNA	70.5%	1.5%
Sequential	81.6%	4.1%

Detectable by cFDNA : T13,18,21, or sex chromosomal aneuploidy
Not detectable by cFDNA: Rare aneuploidies, large deletions and duplications, etc

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Value of NT and Biochemical Screening Beyond Common Aneuploidy

- **Chromosome Abnormalities Other than Common Trisomies**
- **Early Identification of Structural Abnormalities**
  - •Congenital Heart Disease
  - •Other Anomalies
- **Mendelian Genetic Disorders**
- **Poor Pregnancy Outcome**
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  - •Obstetrical Disorders

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Its Not All NT: Value of Biochemistry

Karyotype	Total	NT <3.0 mm	Percent with NT <3.0 mm
Trisomy 21	47	22	46.8%
Trisomy 18	16	6	37.5%
Trisomy 13	6	3	50%
Trisomy 16	1	1	100%
47,XYY	4	3	75%
45,X	9	0	0%
Triploidy	2	2	100%
70,XXYY	1	1	100%
47,XY, +7 / 46,XY	1	1	100%
47,XX, +5 / 46,XX	1	1	100%
47,XY, +13 / 46,XY	1	1	100%
47,XX, +22 / 46,XX	1	1	100%
92,XXYY / 46,XY	1	1	100%
46,XY,inv(1)[p13q21]	1	1	100%
46,XX,t(5;21)[p13;q21.2]	1	1	100%
46,XY,t(5;17)[p31.1;q24]	1	1	100%
46,t(6;9)[q13;p24]	1	1	100%
46,XX,del(4)[4-6] [p14;q27]pat	1	1	100%
Marker chromosome	1	0	0%
Total	97	48	49.5%

Alamillo C Prenatal Diagnosis 2013

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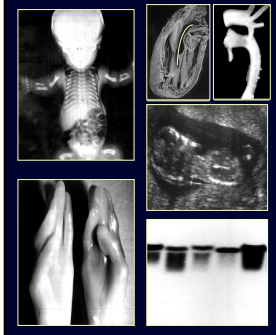
Increased NT and Structural Anomalies



- Cardiac defects / failure
- Intrathoracic compression
- Abnormal lymphatic system
- Neuro-muscular abnormalities
- Altered composition of dermis

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Increased Nuchal Translucency, Normal Karyotype and Structural Anomaly

NT	Anomaly
<95%	<2%
95-99%	3%
3.5-4.4 mm	10%
4.5-5.4 mm	19%
5.5-6.4 mm	24%
> 6.5 mm	46%

Souka, AJOG 2005;192:1005-21

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Early Diagnosis of Structural Anomalies with Ultrasound

Author	Population	N	1st Tri Sensitivity	1st + 2nd Tri Sensitivity
Economides, 1998[1]	Low-risk	1632	65% (11/17)	82% (14/17)
Whitlow, 1999[2]	Unselected	6443	59% (37/63)	81% (51/63)
Chen 2004[3]	≥ 35 y.o.	1609	54% (14/26)	77% (20/26)
Grande 2012	Unselected (nl Karyo)	13,723	49% (96/194)	N/A

1. BJOG 1998
2. BJOG 1999
3. Prenatal Diagn 2004
4. Ult Obs Gyn 2012

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First Trimester Anatomy Screening

Increasing number of first trimester scans
- 11 – 14 wk

Improved high frequency transducers
- Better visualization of fetal anatomy
- First opportunity to detect structural anomalies

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What anatomy can we see at 11-14 weeks?

Organ	Successful visualization (n (%))	
	Transabdominal scan	Transabdominal & transvaginal scan
Head/Brain	1123 (98.16)	1144 (100)
Face	1049 (91.69)	1135 (99.21)
Spine	1111 (97.11)	1141 (99.73)
Abdomen	1108 (96.85)	1142 (99.82)
Stomach	1099 (96.06)	1133 (99.03)
Kidneys	892 (77.97)	1002 (87.58)
Bladder	1035 (90.47)	1136 (99.30)
Extremities	1126 (98.42%)	1144 (100%)

Souka et al. UOG 2004

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First Trimester Anatomic Survey: Detection Rates

- Majority of > 20 published studies = two-staged protocols with an 11-14 wk scan followed by an 18-22 wk scan
- First-trimester detection rates range 16-84%

  Majority reported detection rates > 50%
- After the second trimester ultrasound, two-stage protocols reported detection rates of 48-95%
  - Highest detection rates in studies screening high-risk women
  - In fetuses with multiple anomalies
  - At 13-14 weeks
  - Using a combined TA/TV approach

Timor-Tritsch I, Fuchs K, Monteagudo A, and D'Alton ME. Performing a fetal anatomy scan at the time of first-trimester screening. Obstet Gynecol 2009; 113:402-407.

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First Trimester Structural Anatomy: Detection rates

Almost Always	Usually	Sometimes	Never
Acrania Anencephaly Ectopia cordis Encephalocele Limb Body Wall Alobar Holopros	Gastroschisis Limb reduction Omphalocele	Arthrogryposis Cardiac defects Dandy-Walker Facial cleft Skeletal dysplasia Spina bifida	Pulmonary ACC Bowel

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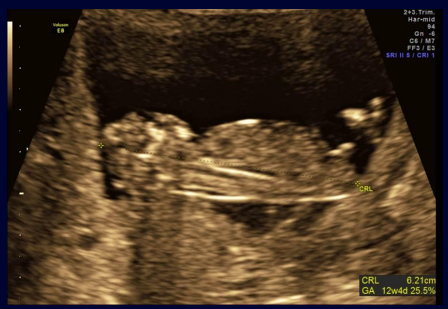
First Trimester Anencephaly



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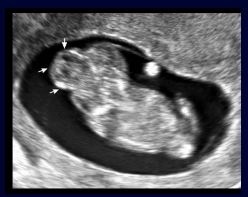
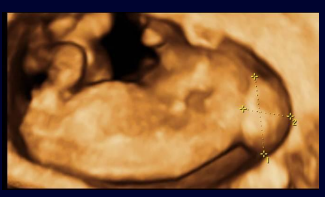
First Trimester Encepalocoel





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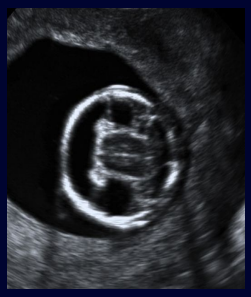
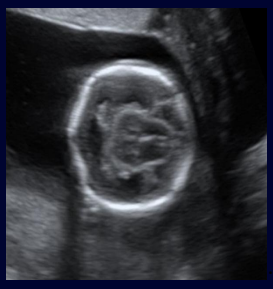
Almost Always Detectable: Alobar Holoprosencephaly





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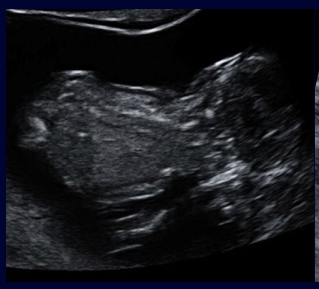
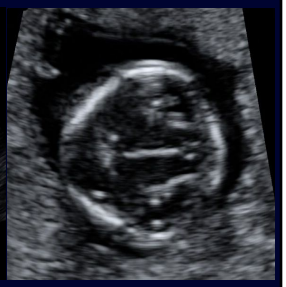
Sometimes Detectable: Spine abnormalities





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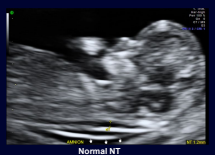
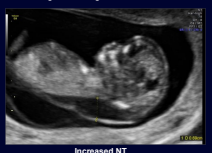
Increased Nuchal Translucency and CHD

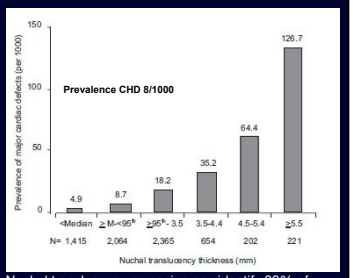


Normal NT

Nuchal translucency screening can identify 30% of fetuses with major CHD using threshold NT of 3.5 mm or ≥ 99th %ile for gestational age



Increased NT



Nuchal translucency screening can identify 30% of fetuses with major CHD using threshold NT of 3.5 mm or ≥ 99th %ile for gestational age

Khalil and Nicolaides, Seminars in Fetal and Neonatal Medicine 2013

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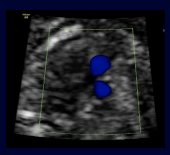
Role of Early Echocardiography

- Cardiac situs
- 4-chamber view
- LVOT
- RVOT
- 3-vessel view
- Aortic arch
- Ductal arch
- SVC and IVC
- Pulmonary veins



Biggest benefit: early reassurance

Johnson and Simpson, Am J Perinatol 2007

Columbia University Medical Center — Carmen and John Thain Center for Prenatal Pediatrics

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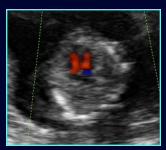
First Trimester Fetal Echocardiography: *Learning Curve*

Parameter	N=103
4-chamber view	100%
Tricuspid regurgitation	100%
Outflow tract crossover	90%
Bifurcating pulmonary artery	81%
3-vessel view	55%
Aortic arch	76%
SVC/IVC	65%
Doppler DV	99%

A complete exam was feasible in 55% of cases in <10 minutes



Abu-Rustum, et al. J Ultrasound Med 2011

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First Trimester Fetal Echocardiography

Overview of Heart Anomalies Detected on First-Trimester Sonography

Authors	GA, wk	No.	Anomalies Detected
DeVore et al (1987)[21]	14	1	VSD, PS
Gembruch et al (1990)[22]	11	1	AVSD
Bronshtein et al (1990)[23]	13–14	2	TOF
Bronshtein et al (1991)[24]	12–16	10	DORV, AVSD, VSD, TOF, HLV, SA-SV
Gembruch et al (1993)[18]	11–16	5	AVSD, PS, SV
Achiron et al (1994)[25]	10–12	8	Tachycardia, ectopia cordis, AVSD, Uhl anomaly, TA, TOF
Carvalho et al (1998)[10]	12	1	AVSD
Areias et al (1998)[26]	12–13	2	AVSD
Baschat et al (1999)[27]	11–14	4	Heart block, AVSD, DORV, TGA, PS
Haak et al (2002)[28]	11–14	10	AVSD, VSD, DORV, HLHS
Huggon et al (2002)[29]	10–14	60	AVSD, HLV, VSD, Ebstein anomaly, TA, PA, LI

- **Sensitivity of first trimester fetal echocardiography for major CHD varies from 10% in low-risk populations to >50% in high-risk groups**

Haak and van Vugt, J Ultrasound Med 2003
Volpe et al, Prenatal Diagnosis 2011
Rossi and Prefumo, Obstet Gynecol 2013

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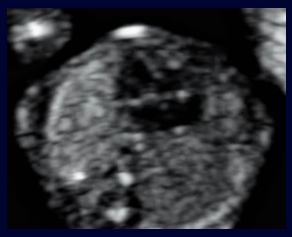
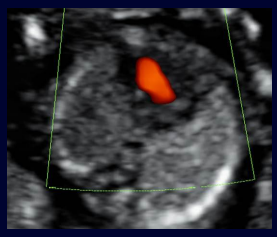
Complete Atrioventricular Canal Defect





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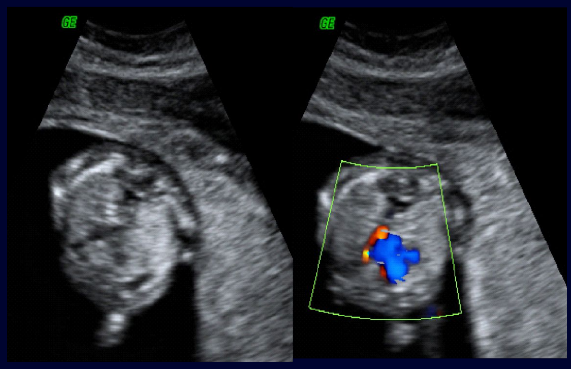
13 weeks

Hypoplastic Left Heart Syndrome



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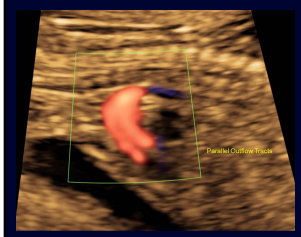
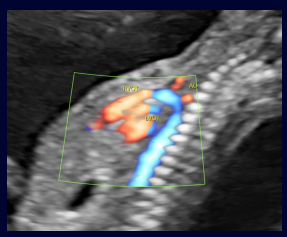
11

Transposition of the Great Arteries





15 weeks

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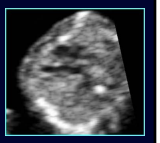
Limitations of Early Echocardiography

Development of CHD later in intrauterine fetal life
- mild pulmonary and aortic stenosis, coarctation, hypoplastic left heart syndrome, rhabdomyomas, cardiomyopathy

Detection of defects that may resolve in utero
- muscular ventricular septal defects

Transabdominal approach may be insufficient
- 92% complete cardiac exam transvaginally versus 84% transabdominally

(Huggon et al, 2002)



11 weeks

Lower diagnostic accuracy
- Lower detection rate and higher false positive rate

(Haak and van Vugt, 2003)

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Genetic Disorders Detected In Fetuses With Enlarged Nuchal Translucency

	Euploid fetuses *(n)*	NT (mm)	Genetic disorders (including neurodevelopmental delay)
Mangione et al., 2001	202	≥ 3mm	0.5%
Souka et al., 2001	1320	≥ 3.5 mm	3.3%
Senat et al., 2002	89	≥ 4 mm	6.4%
Bilardo et al., 2007	425	≥ 95th %	5.4%
Total	2271		4.4%

Bilardo Prenatal Diagnosis 2010

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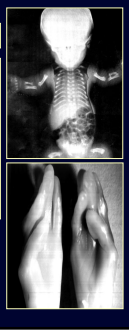
Increased NT and Normal karyotype Genetic Disorders

Genetic Syndromes

- Akinesia deformation
- Noonan syndrome
- Smith-Lemli-Opitz
- Beckwith syndrome
- Fryn syndrome
- Zellweger syndrome
- Trigonocephaly Csyndrome
- Spinal muscular atrophy
- GM1-gangliosidosis



Skeletal Dysplasias

- Thanatophoric dysplasia
- Jarcho-Levine syndrome
- Achondrogenesis
- Asphyxiating thoracic dystrophy
- Campomelic dysplasia
- Nance Sweeney Syndrome
- Robert syndrome
- VACTER association
- EEC syndrome

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Elevated NT ≥3.5mm

	N	Pathogenic Mutation	VOUS	Total Abnormal
Noonan Testing	483	5.2%	2.3%	7.5%
Microarray	291	2.7%	2.4%	5.1%
Total		7.9%	4.7%	12.6%

Coletta et al; AJOG 2014

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Noonan Syndrome

Overall Frequency: 1:1000 -1:2500
Frequency with NT > 4 mm 2-5:100

Mutated Gene	%
PTPN11	50%
SOS1	10%-13%
RAF1	3%-17%
KRAS	<5%
NRAS	rare
BRAF	<2%
MAP2K1	<2%
Overall	75%-80%

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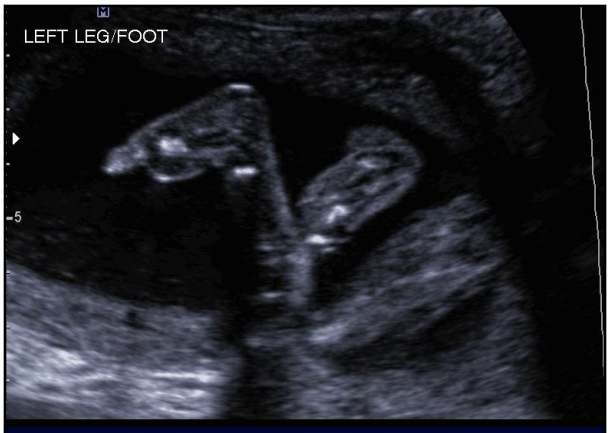

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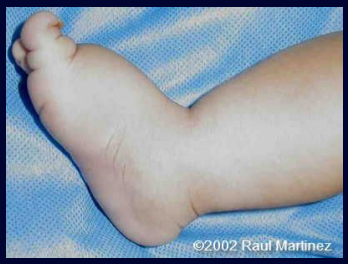

FOXC2

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Prevalence and Etiology of Congenital Abnormalities (It's Not All Down Syndrome)

	Prevalence
Common Trisomies (21,18,13)	0.2%
Chromosome Abnormalities Other than Common Trisomies	0.4%
Microdeletons and duplications	1.5%
Mendelian Genetic Disorders	0.4%
Structural Congenital Abnormalities	3.0%
Congenital Heart Disease	0.3%

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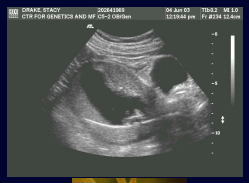
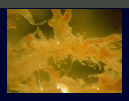
Invasive Testing Methods
What is the Risk?





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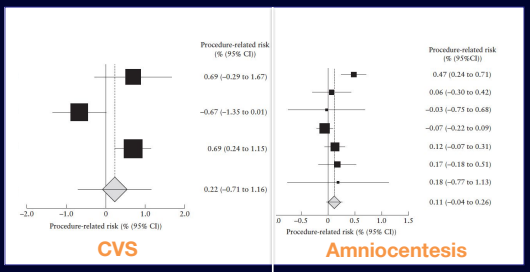
Systematic Review: Risk of Diagnostic Procedure



Risk of Procedure Induced Loss 1:455

Risk of Procedure Induced Loss 1:909

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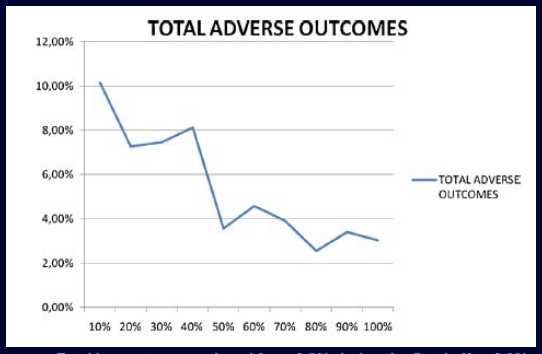
Akolekar Ult Obs Gynecol 2015

Impact of Experience on Amniocentesis Outcomes



Fetal loss rate was reduced from 0.5% during the first half to 0.3%

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Margioula-Siarkou: Eur J of Obs and Gyn and Repro Biol 2012

Decreasing CVS Loss Rates With Experience (NICHD)

	N CVS	Total SAB RATE	Excess SAB Rate CVS over Amnio
1985 – 87 •Rhoads et al., NEJM, 1989	2278	3.2%	0.8% *(NS)*
1987 – 89 •Jackson et al., NEJM, 1992	3873	2.4%	
1997 – 2001 •Philip et al Obstet/Gynecol, 2004	1878	1.3%	

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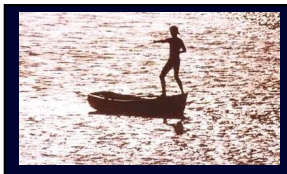

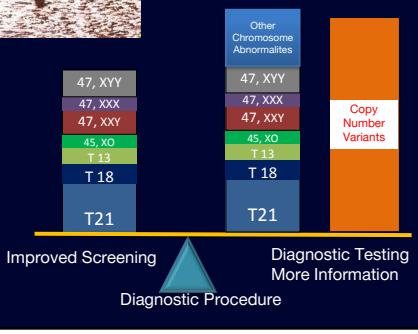

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Overall Risk of a Congenital Abnormality (Its not all Down Syndrome)

	Prevalence
Common Trisomies (21,18,13)	0.2%
Chromosome Abnormalities Other than Common Trisomies	0.4%
Microdeletons and duplications	1.0%
Mendelian Genetic Disorders	0.4%
Structural Congenital Abnormalities	3.0%
Congenital Heart Disease	0.3%
Poor Pregnancy Outcome	

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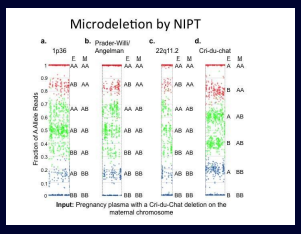
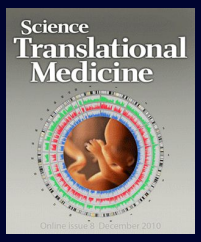
Where Are We Going ?

Non-invasive sequencing of the fetal genome is likely to be a reality in the not-too-distant future

Tremendous counseling and ethical issues

- Uncertain Reassurance
- Counseling
- Scope Creep





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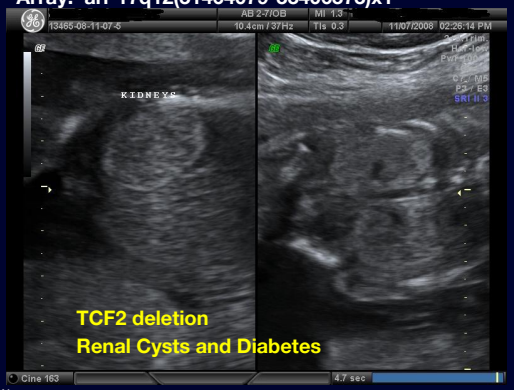
CVS: Normal Karyotype
Array: arr 17q12(31464079-33406373)x1



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Conclusions

- Prenatal aneuploidy screening is intended to identify women at the highest risk for a fetal chromosome abnormality
-
  - There are presently two approaches to screening in the first trimester each with its own advantages and disadvantage:
    - Combined Screening using biochemistrty and nuchal translucency:
      - Advanatage:
        - » low cost
        - » Includes first trimester scan
        - » Nuchal translucency identifies additional structural and genetic disorders
      - Disadvantage:
        - » Sensitivity only 85- 90%; Specificty 97%

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Conclusions (cont.)

- Cell free DNA
  - Advantage
    - » Sensitivity for trisomy 21 over 99%; Specificty 99.9%
  - DIsadvanatge
    - » Expensive
- All patients should be informed of the availability and value of fetal diagnostic Testing by CVS or amniocentesis
  - Identifies all chromosome abnormalities
  - Identifies sub chromosomal microdeletions and duplications
- Pretest counseling is imperitive

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Key References

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Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. *AJOG*, 2005; 192:1005-21.

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