Perinatal Genetics

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Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine

Disclosure Statement:

- Dr. Edith Cheng has no relevant financial relationships with ineligible companies to disclose.

Perinatal Genetics: Technology and Science

FETAL ACCESS

- IMAGING
  - Ultrasound 2d, 3D, 4D
  - Fetal MRI
  - Fetal low dose CT
- Amniocentesis
- Chorionic Villus Sampling
- Fetal cordocentesis
- Fetal tissue biopsy
- Fetal surgery/therapy
- Preimplantation Genetic (IVF)
  - PGT-A (aneuploidy screening)
  - PGT-M (monogenic disorder)
  - PGT-SR (balanced translocation)

FETAL INVESTIGATION

- Cytogenetic
- Biochemical
  - Maternal Serum Screening
- Human Genome Project
- Molecular Technology/Discoveries
  - Next Gen Sequencing
  - Exome sequencing
  - NIPT
- Immunology
  - Maternal <-> fetal tolerance
  - Maternal <-> fetal conversations

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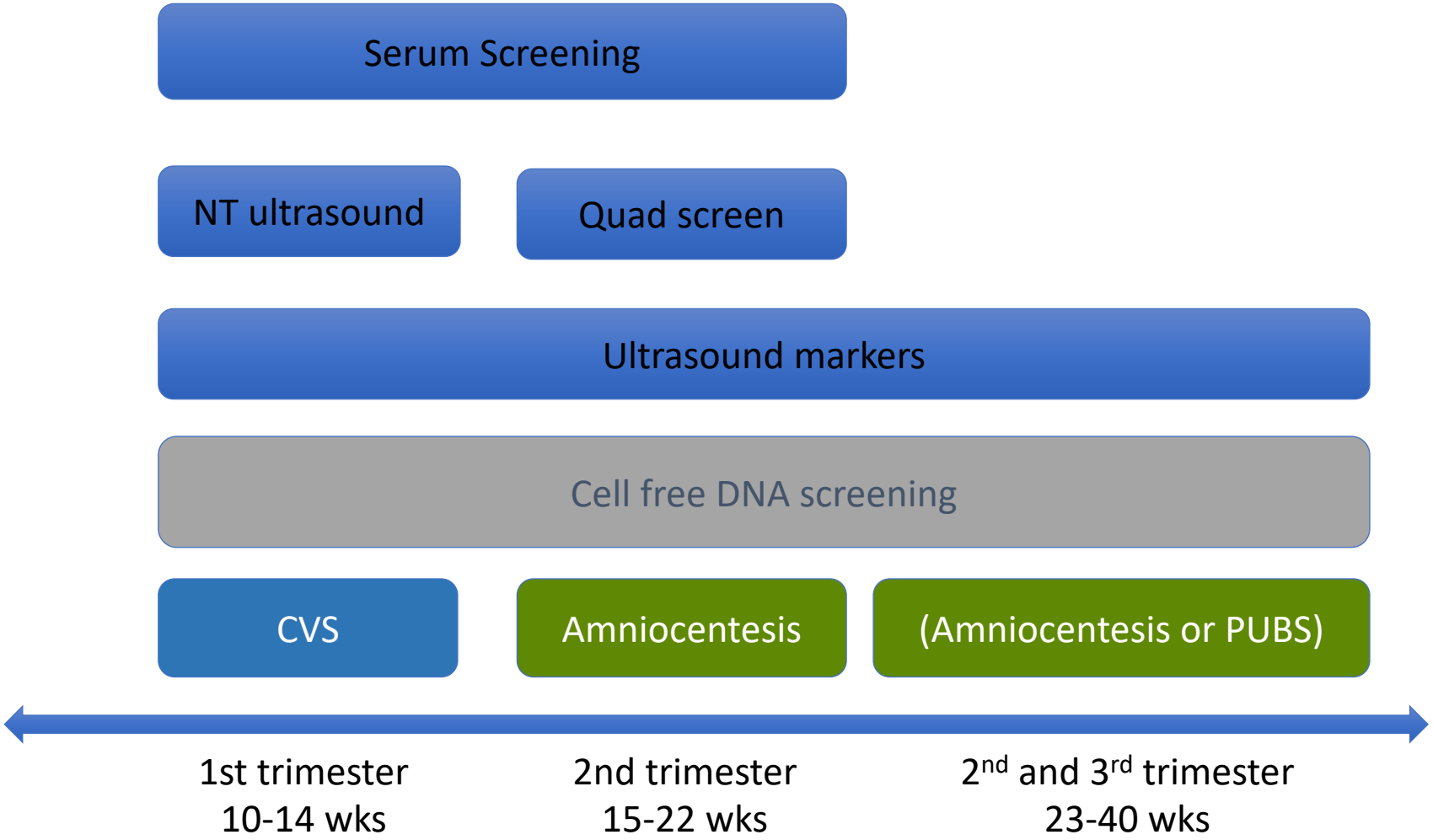
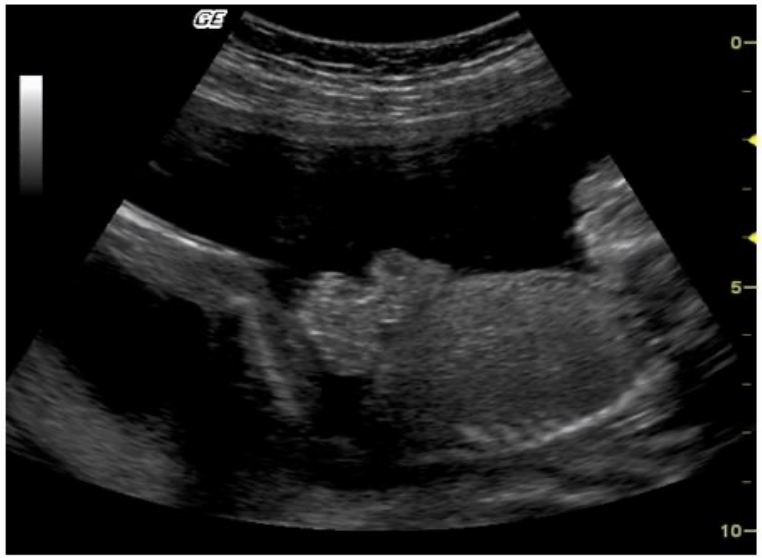
Prenatal Screening Options



Prenatal Imaging – Ultrasound – Important Screening Tool

3% pregnancies will have abnl ultrasound
75% malformations found in ”Low Risk” population

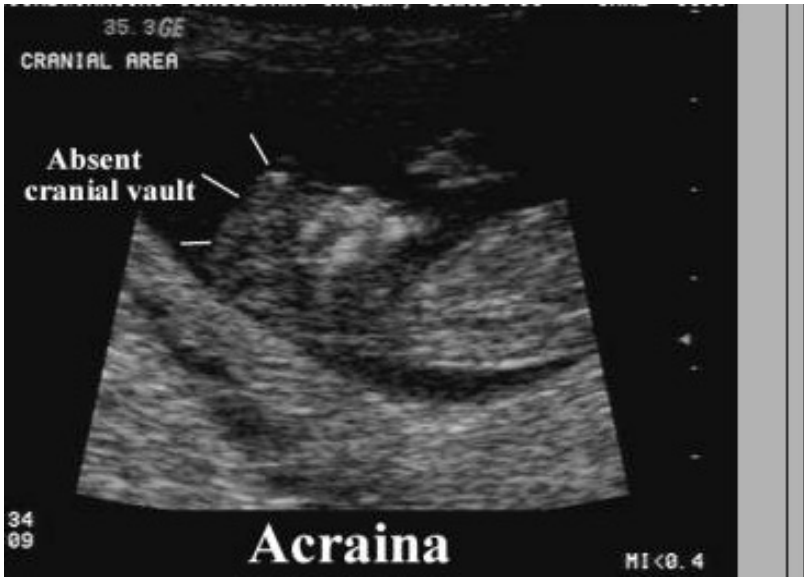
1994 RADIUS 1st randomized control trial low risk
35% screen group 11% control group
1999 EUROFETUS
56% sensitivity -> major and minor malformations
2002 Levi S. 36 studies 900,000 fetuses
40% detection rate

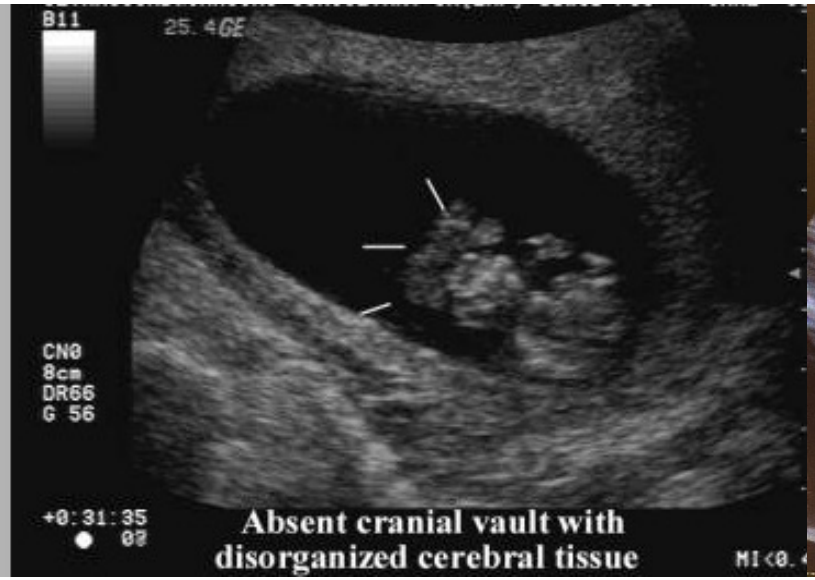


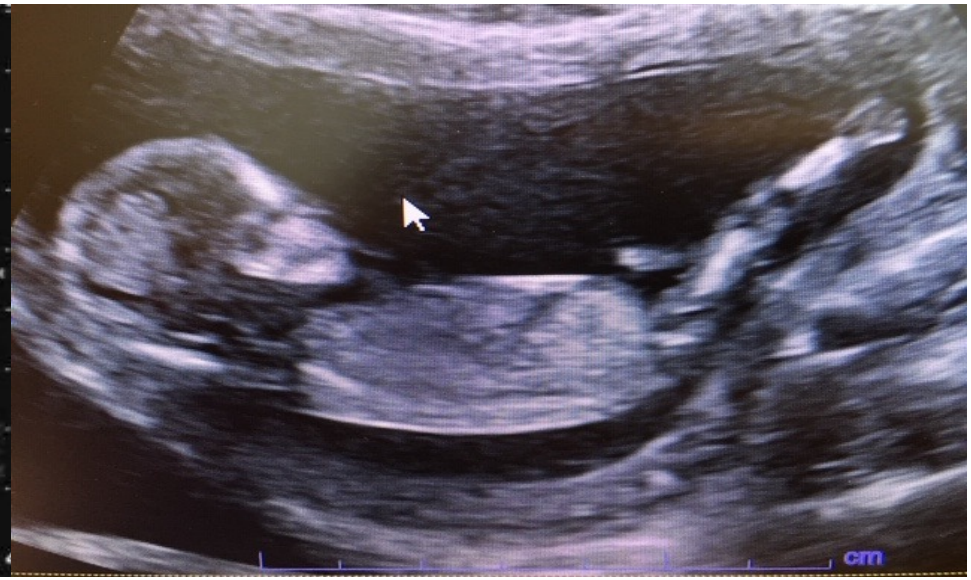
Management Options: Fetal and Maternal Impact
Early termination – lethal anomalies – maternal safety
Fetal intervention - treat/delay disease progression

Pregnancy dating accuracy
Identifies multiple gestations
determines chorionicity
mono-di tiwns → TTTS risk
Abnormal placentation
C/section scar ectopic

Prenatal Imaging Ultrasound 1st trimester







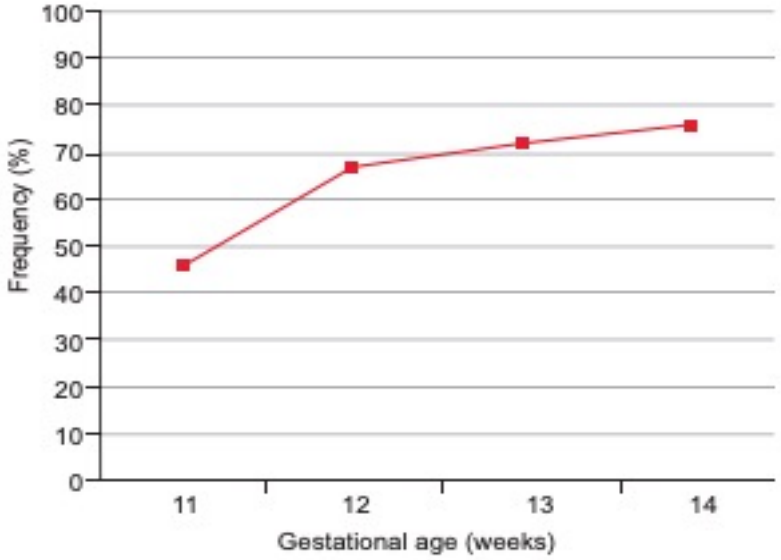


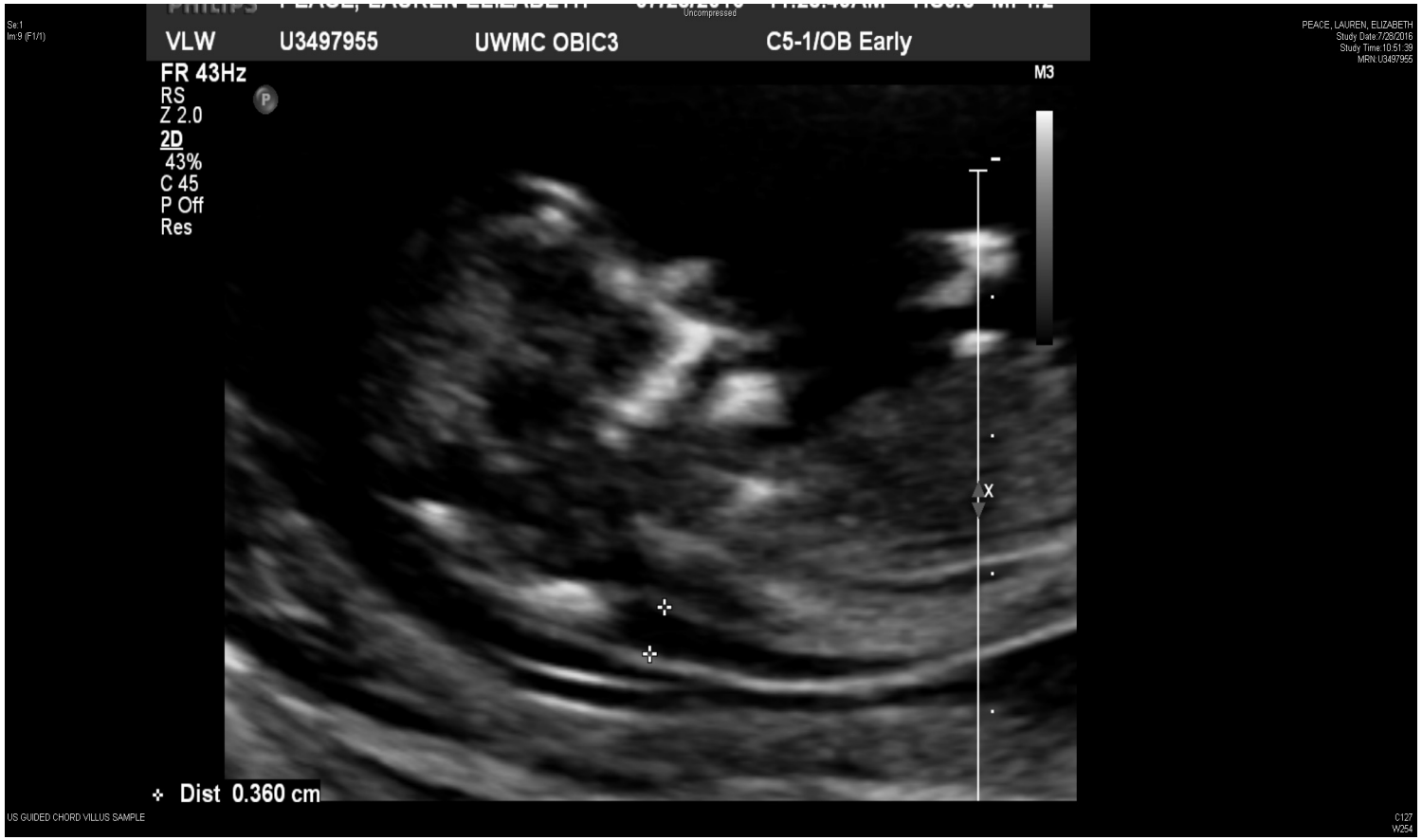
Fig. 3. Detection rates from 11–14 weeks of gestation.
Rossi. First-Trimester Ultrasonography. Obstet Gynecol 2013.

Detection Rate for Malformations in the First Trimester

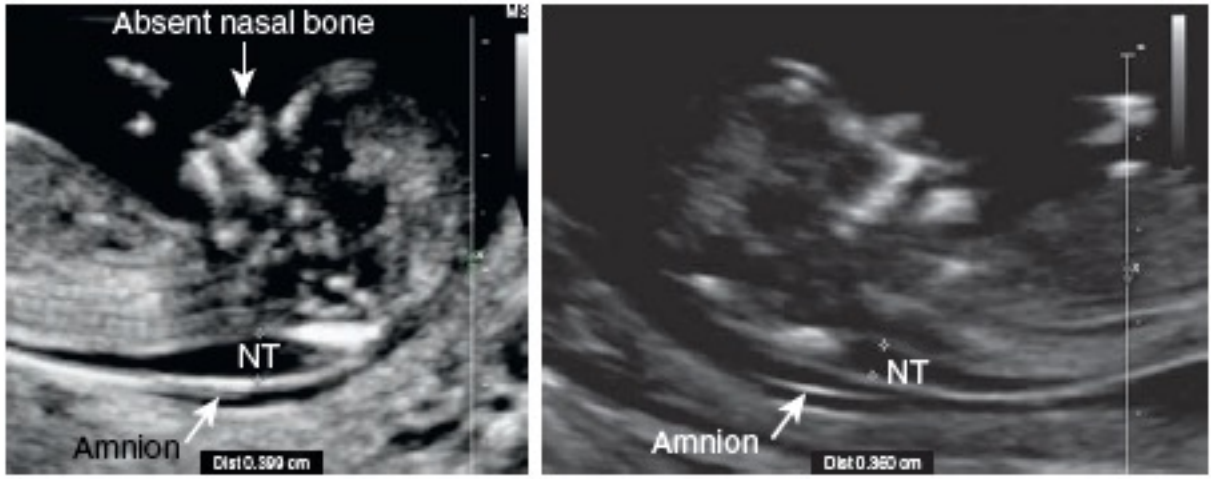
100%	Acrania, anencephaly, ectopia cordis
50 – 99%	Cystic Hygroma, omphalocele, holoprosencepaly, encephalocele, limb abnormalities, megacystis, major heart defect (HLHS)
1 – 49%	ONTD, hydrocephalus, skeletal dysplasia, arthrogryposis
0%	ACC, bladder exstrophy, CPAM, duodenal atresia, renal agenesis

Rossi CA and Prefumo F. Obstet Gynecol 2013

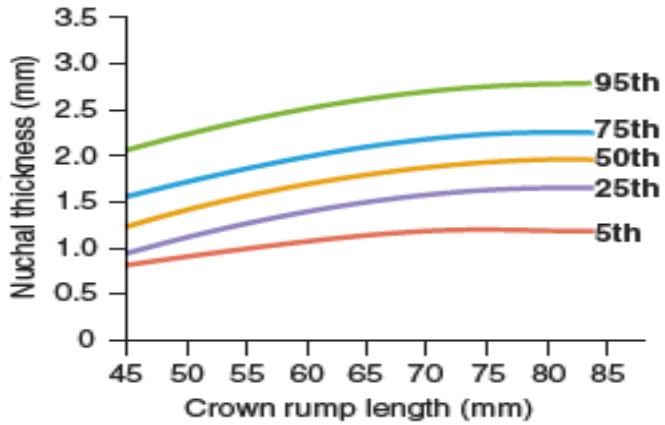
Role of Increased Nuchal Translucency



- 75% DS fetuses ->increased NT
- Other defects
  - Turner Syndrome
  - other cytogenomic disorders
  - cardiac defects
  - skeletal dysplasia – severe
  - alpha thal major (Barts)
  - other



45 50 55 60 65 70 75 80 85



Nuchal thickness Crown rump length (mm)	***Chromosomal defects***	***Fetal death***	***Major fetal abnormalities***	***Alive and well***
<95th %ile	0.2%	1.3%	1.0%	97%
95th–99th %iles	3.7%	1.3%	2.5%	93%
3.5–4.4 mm	21.1%	2.7%	10.0%	70%
4.5–5.4 mm	33.3%	3.4%	18.5%	50%
5.5–6.4 mm	50.5%	10.1%	24.2%	30%
>6.5 mm	64.5%	19.0%	46.2%	15%

Normal karyotype

•**Fig. 18.7** Interpretation of Nuchal Thickness and Relationship to Gestational Age and Risk for Fetal Outcomes. *NT, nuchal thickness.* (Adapted from Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal thickness with normal karyotype. *Am J Obstet Gynecol.* 2005;192: 1005–1021.)

› Ultrasound Obstet Gynecol. 2017 May;49(5):592-598. doi: 10.1002/uog.15961. Epub 2017 Apr 5.

Increased nuchal translucency thickness and risk of neurodevelopmental disorders

S G Hellmuth [1 2], L H Pedersen [3 4], C B Miltoft [1 2], O B Petersen [3], S Kjaergaard [5], C Ekelund [1], A Tabor [1 2]

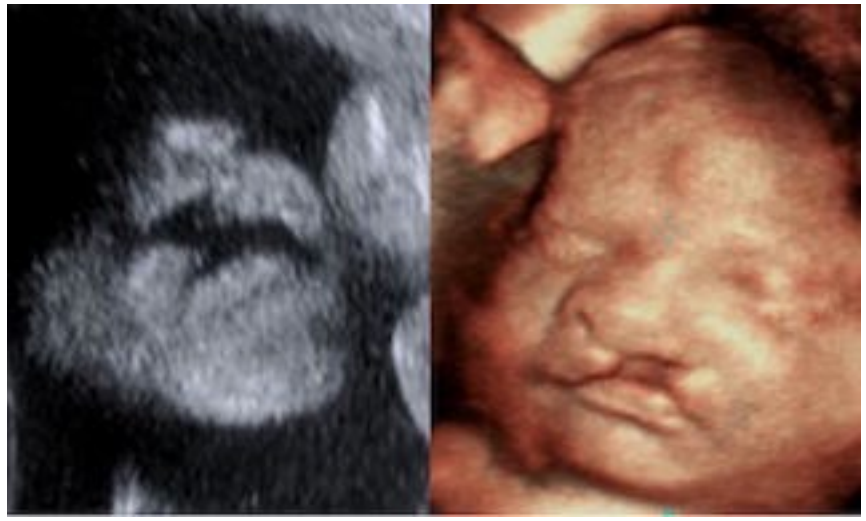
Normal karyotype and US

Table 2 Neurodevelopmental outcome in study groups of euploid children according to prenatal nuchal translucency (NT) thickness

Outcome	*All* (n = *222 505*) (n)	*Reference Group 1: NT < 95th percentile* (n = *217 103*) (n (%))	*Group 2: NT 95th–99th percentile* (n = *4760*)		*Group 3: NT > 99th percentile* (n = *642*)	
			n (%)	*OR (95% CI)*	n (%)	*OR (95% CI)*
No impairment	212 081	206 932 (95.32)	4538 (95.34)		611 (95.17)	
Any impairment	10 424	10 171 (4.68)	222 (4.66)	1.00 (0.87–1.14)	31 (4.83)	1.03 (0.72–1.48)
Intellectual disability	116	110 (0.05)	4 (0.08)	1.72 (0.63–4.67)	2 (0.31)	6.16 (1.51–25.0)
ASD	706	686 (0.32)	15 (0.32)	1.00 (0.60–1.66)	5 (0.78)	2.48 (1.02–5.99)
Childhood autism	338	327 (0.15)	9 (0.19)	1.10 (0.57–2.14)	2 (0.31)	1.82 (0.45–7.32)
Cerebral palsy	547	533 (0.25)	11 (0.23)	0.94 (0.52–1.71)	3 (0.47)	1.91 (0.61–5.95)
Epilepsy	1148	1120 (0.52)	23 (0.48)	0.94 (0.62–1.42)	5 (0.78)	1.51 (0.63–3.66)
Febrile seizures	8141	7950 (3.66)	174 (3.66)	1.00 (0.86–1.16)	17 (2.65)	0.72 (0.44–1.16)
ICD-10 G-group diagnosis	3701	3591 (1.65)	89 (1.87)	1.13 (0.92–1.40)	21 (3.27)	2.01 (1.30–3.11)

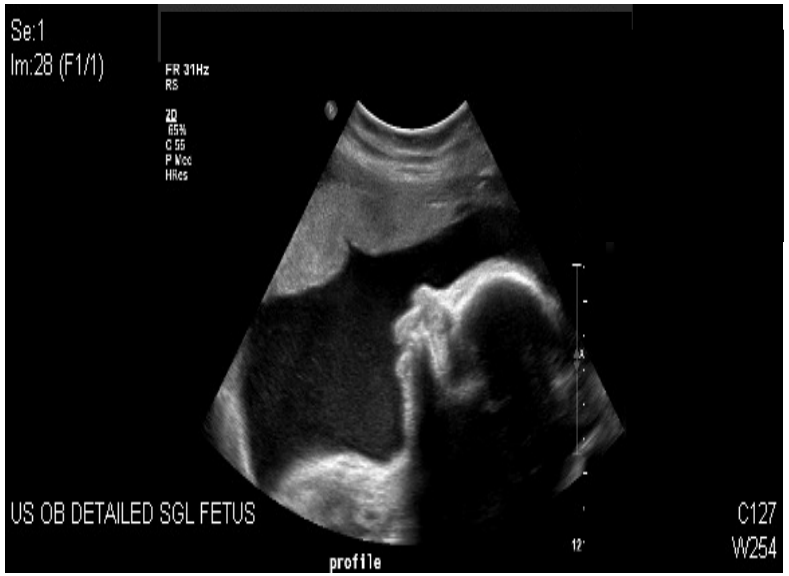
ASD, autism spectrum disorder; ICD-10, International Classification of Diseases, tenth revision; OR, odds ratio.

Prenatal Diagnosis - Imaging

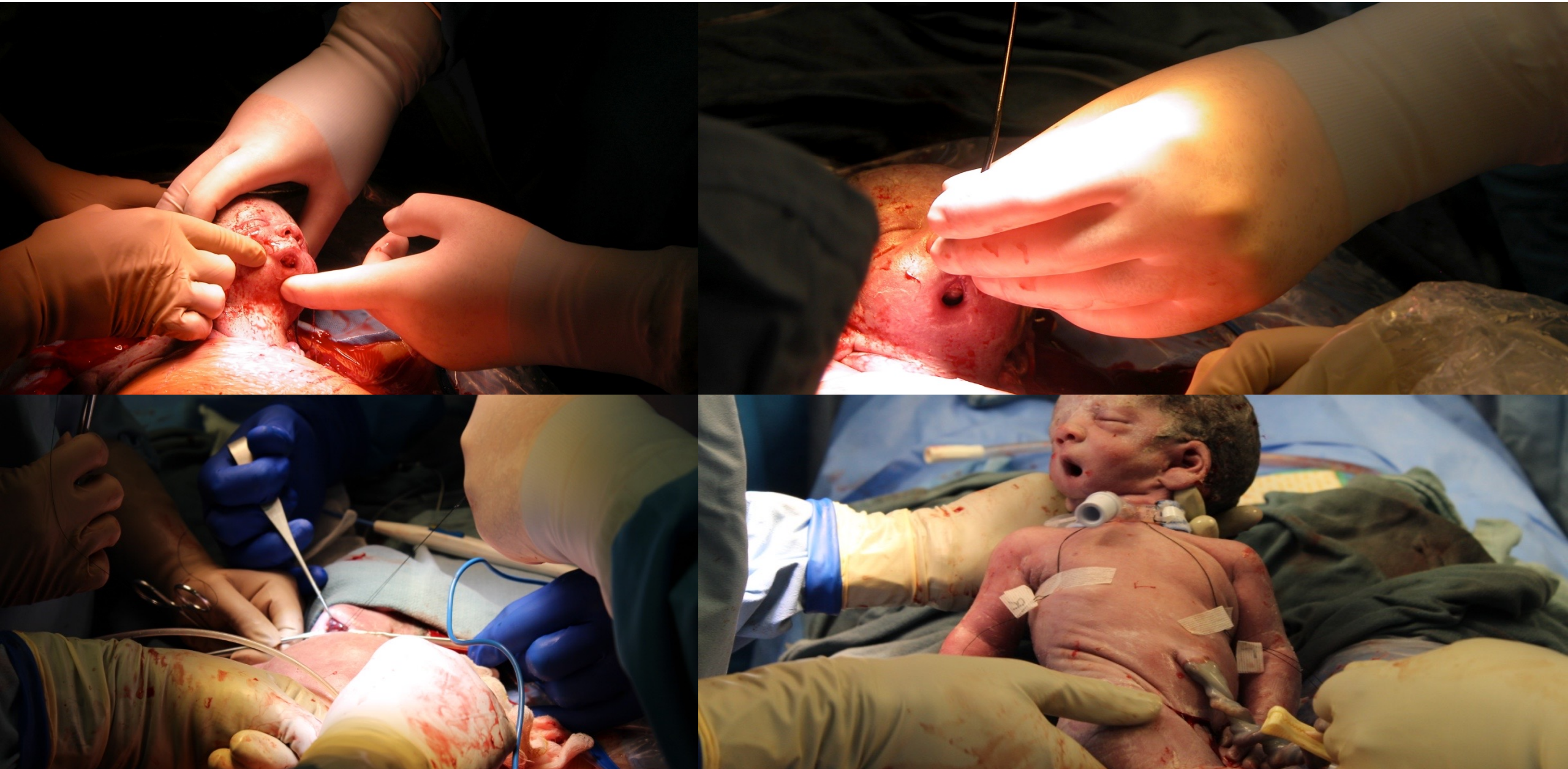


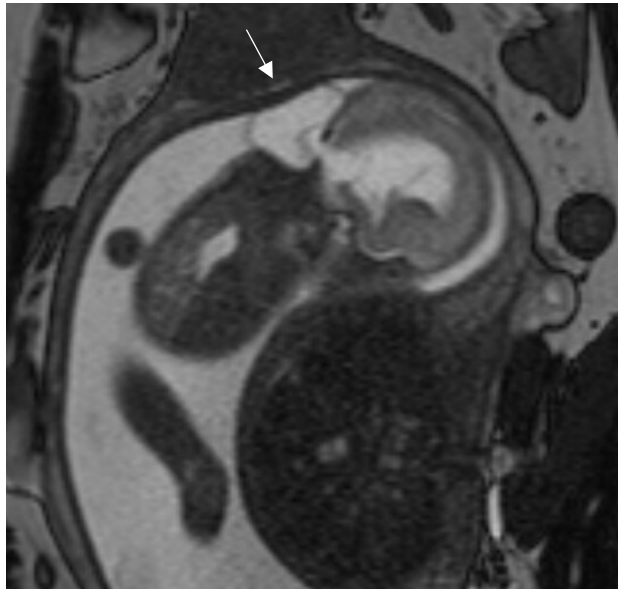
2 D and 3 D Ultrasound

Prenatal Dysmorphology

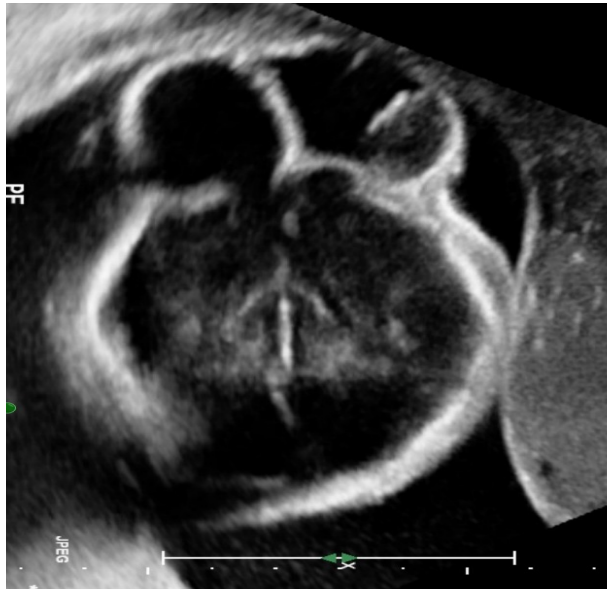


EXIT PROCEDURE – ACQUIRING AIRWAY PRIOR TO SEPARATION FROM THE PLACENTA





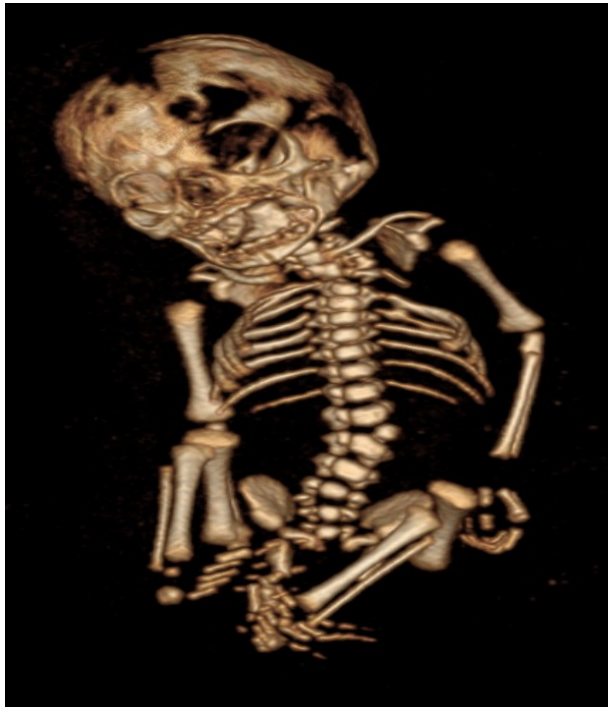
Prenatal T2 weighted MRI at 21 weeks, posterior meninomyelocele

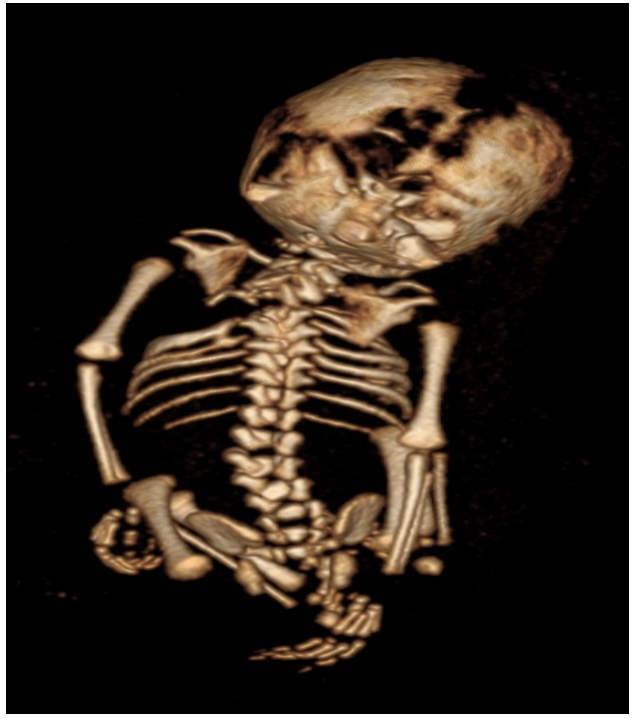


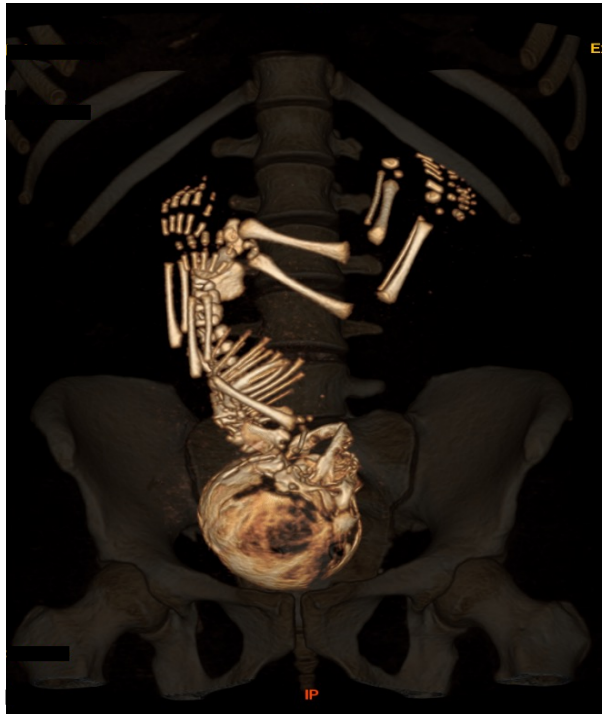
Prenatal ultrasound at 28 weeks

FETAL MRI

LOW DOSE CT SCAN







Maternal Serum Screening

1970's:	High AFP for NTD
1984:	Low MSAFP + maternal age
1988:	Triple Screen
1990:	**1st trimester screening** Nuchal Thickening (NT) PAPP-A ß-hCG
1992:	**Quad screen** (Inhibin A)
1999:	**Integrated Screen** 1st/2nd trimester

Quad Screen
2nd Trimester Screening

	AFP	uE3	hCG	INH	
Down Syndrome					
Trisomy 18	↓	↓	↑	↑	
Neural Tube Defect:	↓	↓	↓	↑	*Gold Standard*
Smith Lemli Opitz		↓			< 0.65 MoM
X- linked ichthyosis		↓			< 0.1 MoM

Obstetrical
Placental Health
Twins
Fetal Demise
IUGR
Pre-Eclampsia

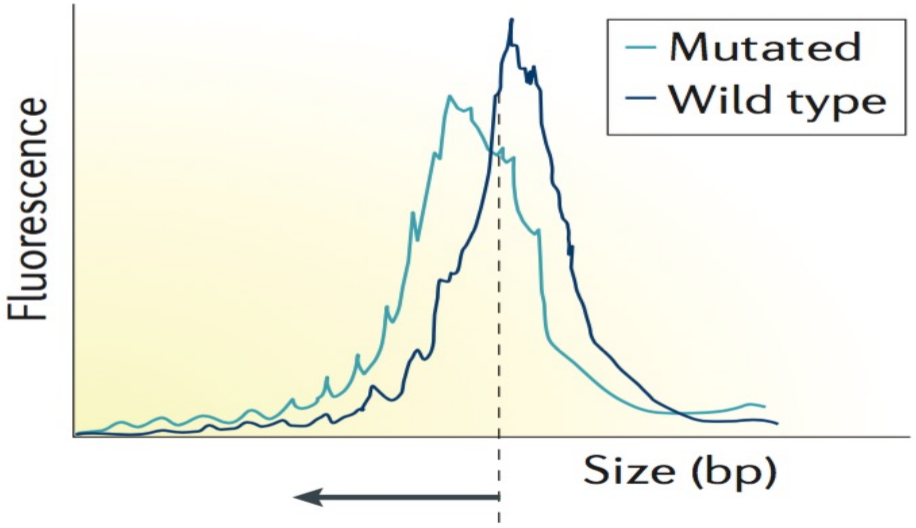
THE LANCET
Volume 350, Issue 9076, 16 August 1997, Pages 485-487

Early Report

Presence of fetal DNA in maternal plasma and serum

MRCP, Dr Y M Dennis Lo [a], Noemi Corbetta [d], MD Paul F Chamberlain [b], MRCOG Vik Rai [b], PhD Ian L Sargent [b], FRCP Prof Christopher WG Redman [b], FRCPath James S Wainscoat [c]

Fetal fraction prediction exploits the size difference between maternal and fetal cfDNA



Modified from: Wan JC, et al.. *Nat Review Canc* 2017;17:223-38

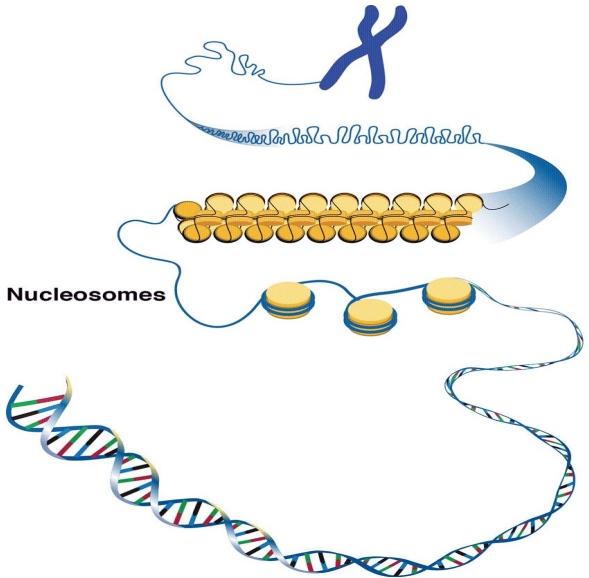
Cell-free DNA fragments released are small

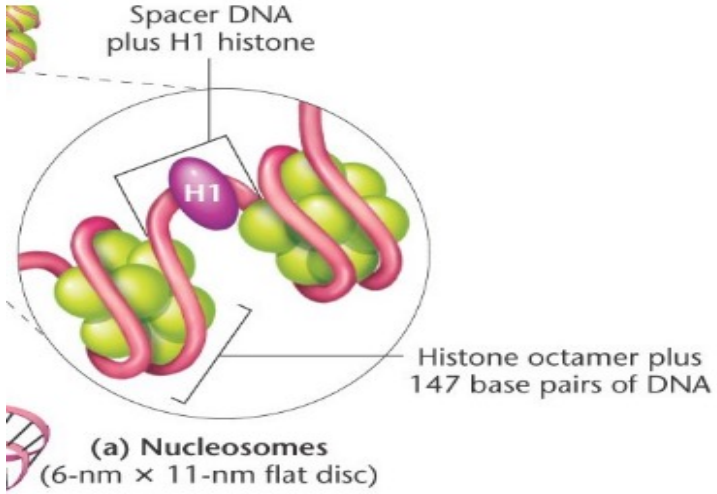
Maternal cell-free DNA peaks at 167 bp

147bp DNA nucleosome + 20bp spacer DNA (H1 linker)

Fetal DNA is smaller on average

147bp DNA nucleosome





ESTABLISHED IN 1812 APRIL 23, 2015 VOL. 372 NO. 17

Cell-free DNA Analysis for Noninvasive Examination of Trisomy

Mary E. Norton, M.D., Bo Jacobsson, M.D., Ph.D., Geeta K. Swamy, M.D., Louise C. Laurent, M.D., Ph.D., Angela C. Ranzini, M.D., Herb Brar, M.D., Mark W. Tomlinson, M.D., Leonardo Pereira, M.D., M.C.R., Jean L. Spitz, M.P.H., Desiree Hollemon, M.S.N., M.P.H., Howard Cuckle, D.Phil., M.B.A., Thomas J. Musci, M.D., and Ronald J. Wapner, M.D.

Table 2. Test Performance for Trisomy 21 in the Primary Analysis Cohort, According to Maternal Age and Risk.*

Variable	Standard Screening	Cell-free DNA Testing		
	All Patients (N=15,841)	All Patients (N=15,841)	Maternal Age <35 Yr (N=11,994)	Low Risk (N=14,957)†
True positive — no.	30	38	19	8
True negative — no.	14,949	15,794	11,969	14,941
False positive — no.	854	9	6	8
False negative — no.	8	0	0	0
Sensitivity (95% CI) — %	78.9 (62.7–90.4)	100 (90.7–100)‡	100 (82.4–100)	100 (63.1–100)
Specificity (95% CI) — %	94.6 (94.2–94.9)	99.9 (99.9–100)§	99.9 (99.9–100)	99.9 (99.9–100)
Positive predictive value (95% CI) — %	3.4 (2.3–4.8)	80.9 (66.7–90.9)¶	76.0 (54.9–90.6)	50.0 (24.7–75.3)
Negative predictive value (95% CI) — %	99.9 (99.9–100)	100 (99.9–100)¶	100 (99.9–100)	100 (99.9–100)
Positive likelihood ratio	14.6	1755.9	1995.8	1868.6
Negative likelihood ratio	0.22	0	0	0

* P values are for the comparison between standard screening and cell-free DNA screening in the primary analysis cohort.
† Low risk was defined as a mid-trimester risk of trisomy 21 of less than 1 in 270 on standard screening.
‡ P=0.008
§ P<0.001
¶ P=0.005.

Outcomes in noninformative cfDNA testing

13 aneuploidies

• Trisomy 21	3
• Trisomy 18	1
• Trisomy 13	2
• Triploidy	4
• Tri-16 mosaic	1
• Other	2

All detected by serum screening

Non informative	3%
Fetal fraction < 4%	1.2%
Mat wt 93.7 kg vs. 65.8 kg	
Fetal fraction not measurable	0.5%
High variance/failure	1.3%

Norton et al. NEJM. 2015

OBSTETRICS

Chromosomal abnormalities not currently detected by cell-free fetal DNA: a retrospective analysis at a single center

AJOG 2016; 214;729.e1-11

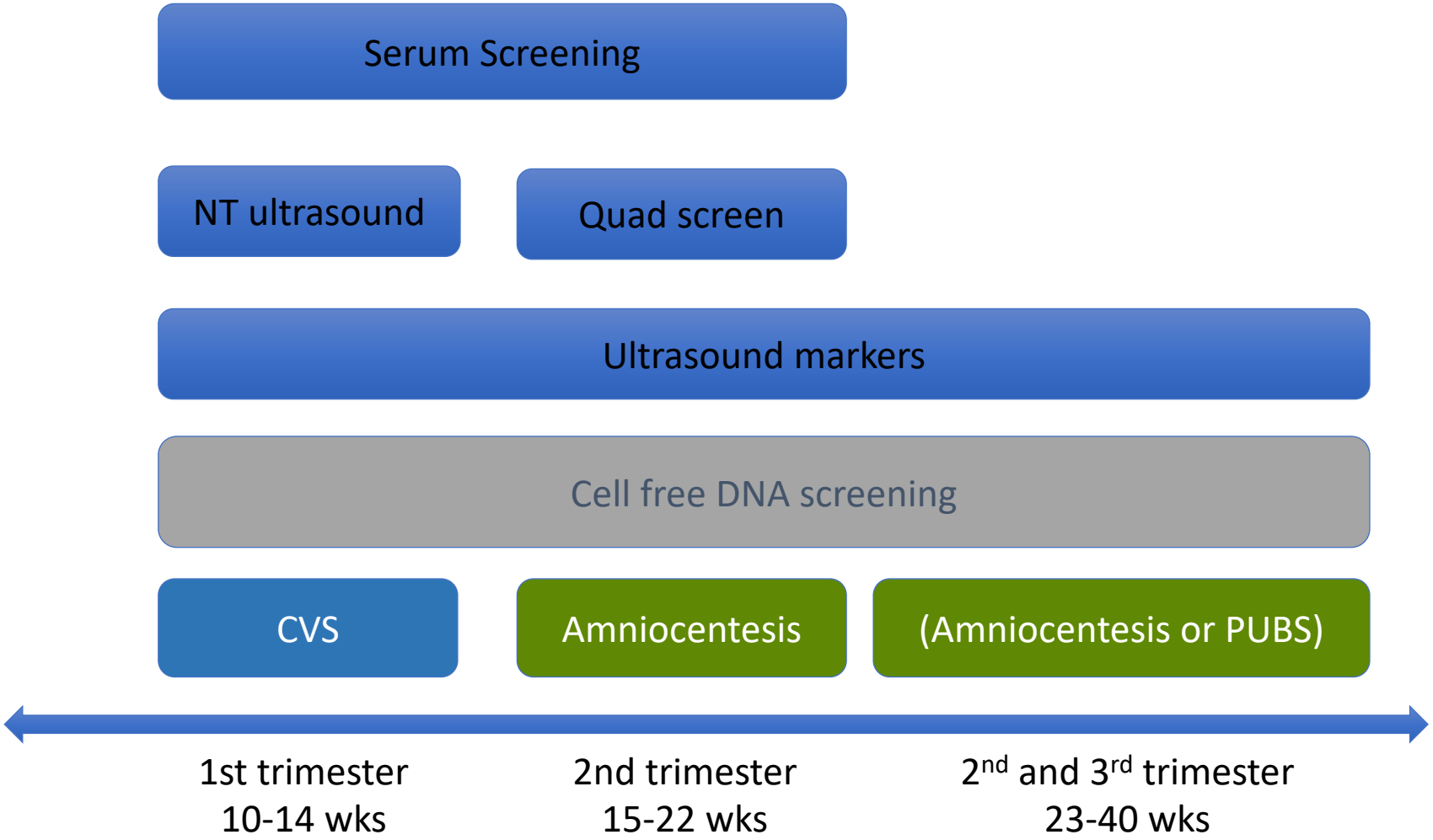
Hagit Shani, MD; Tamar Goldwaser, MD; Jennifer Keating, MS; Susan Klugman, MD

- 3182 diagnostic procedures: 2009 – 2014
  - AMA and/or ultrasound or screening abnormalities
  - All had karyotype 1/3 had microarray
  - 220 genomic abnormality (7%)
    - 125 (57%) common autosomal trisomies : 21, 13, 18, sex chromosome
    - 23 mosaic karyotypes
      - 8 (21 and 13) 5 (sex chromosomes) *10 (other*)
    - 5 triploidy
    - 19 unbalanced translocations
    - 1 rare autosomal trisomy
    - 47 clinically significant micorarray findings
- **Conclusion: Current cfDNA would not have detected 43% of clinically significant genomic changes**
  - **79% had abnormal serum screening and/or abnormal ultrasound**
  - **21% were AMA only**

cfDNA in Maternal Serum
Benefits and Challenges

- Late pregnancy with birth defects
- Avoid invasive procedure and risks
- Accepts limitations of results
- Placental DNA assumes surrogate for fetus
  - “liquid CVS”

Prenatal Screening Options



Prenatal Screening – Access - Equity

ACOG
The American College of Obstetricians and Gynecologists

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 226 *(Replaces Practice Bulletin 163, May 2016, Reaffirmed 2018)*

Committee on Practice Bulletins—Obstetrics, Committee on Genetics, and Society for Maternal-Fetal Medicine. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics and Committee on Genetics, and the Society for Maternal-Fetal Medicine in collaboration with Nancy C. Rose, MD, and Anjali J. Kaimal, MD, MAS, with the assistance of Lorraine Dugoff, MD, and Mary E. Norton, MD, on behalf of the Society for Maternal-Fetal Medicine.

Screening for Fetal Chromosomal Abnormalities

▶ ***What information should be included when counseling patients regarding the option of prenatal screening for chromosomal abnormalities?***

There is not one screening test that performs optimally in all clinical scenarios and all screening tests detect fewer abnormalities than diagnostic testing that include microarray analysis. Health care professionals should be

Clinical Considerations and Recommendations

▶ ***Who should be offered testing for chromosomal abnormalities?***

Screening (serum screening with or without NT ultrasound or cell-free DNA screening) and diagnostic testing (CVS or amniocentesis) for chromosomal abnormalities should be discussed and offered to all patients early in pregnancy regardless of maternal age or baseline risk.

If a patient chooses screening for aneuploidy, only one screening approach should be used. Analyte screening and cell-free DNA screening should not be sent concurrently as this strategy is not cost-effective and simultaneous, seemingly discordant results can be more distressing to patients than screen positive analyte results followed by reassuring cell-free DNA screening (42, 43).

J Matern Fetal Neonatal Med. 2018 Oct 1:1-7. doi: 10.1080/14767058.2018.1519541. [Epub ahead of print]

Decisional regret in women receiving high risk or inconclusive prenatal cell-free DNA screening results.

Gammon BL[1,2], Jaramillo C[1], Riggan KA[1], Allyse M[1,3].

… A growing number of women are offered cfDNA screening for an increasing broad range of chromosomal and microdeletion syndromes. However, research shows that the very low false positive rate attributed to cfDNA for trisomy 21 does not apply to other conditions

- would not elect cfDNA in future - 1/3
- limit scope of panel or screen only under specific circumstances - 1/3
- Misleading information
  - Prior to accepting screening – inadequate pretest discussion
  - Receiving results
- Clinical dialog misleading when
  - Screening offered
  - Results reported
  - Explanation/lack of information about false positive results
- Suggested improvement
  - Mode of offering cfDNA screening should be reassessed

Obstet Gynecol Clin North Am. 2018 Mar;45(1):27-39. doi: 10.1016/j.ogc.2017.11.001.

Cell-Free DNA: Screening for Single-Gene Disorders and Determination of Fetal Rhesus D Genotype.

Gerson KD[1], O'Brien BM[2].

Table 1
Conditions diagnosed using cell-free DNA

Aneuploidy	Trisomy 21 Trisomy 18 Trisomy 13 Turner syndrome XXX Klinefelter syndrome XYY
Blood group systems	Rh Kell
Autosomal dominant disorders[a]	Achondroplasia Thanatophoric dysplasia Apert syndrome Myotonic dystrophy Huntington disease
Autosomal recessive disorders[a]	Cystic fibrosis Congenital adrenal hyperplasia Sickle cell anemia β-Thalassemia Spinal muscular atrophy Gaucher disease Wilson disease
X-linked recessive disorders[a]	Hemophilia Duchenne muscular dystrophy Becker muscular dystrophy

[a] Examples are included but not limited to these conditions.

Cell Free DNA

More than prenatal diagnosis

Biological explanations for discordant noninvasive prenatal test results: Preliminary data and lessons learr

Prenatal Diagnosis. 2018;38:445–458.

Louise Wilkins-Haug[1] | Chengsheng Zhang[2] | Eliza Cerveira[2] | Mallory Ryan[2] | Adam Mil-homens[2] | Qihui Zhu[2] | Honey Reddi[2] | Charles Lee[2] | Diana W Bianchi[3,4]

TABLE 1 Patient samples received, processed, and presumptive explanation for discordancy

Sample ID	cfDNA result	Fetal or neonatal karyotype	Maternal blood (predelivery)	Maternal blood (postdelivery)	Cord blood	Placenta biopsy 1	Placenta biopsy 2	Placenta biopsy 3	Placenta biopsy 4	Presumptive explanation
BWH001	del22q	46, XX	N/A	N/A	√	√	√	√	N/A	CPM for del 22q
BWH002	MX	46, XY/45, X	N/A	√	N/A	√	√	√	N/A	Fetal mosaicism
Tufts001	T13, T18	46, XY	N/A	√	√	√	√	√	N/A	CPM for trisomy 13
Tufts002	T13	46, XY	N/A	√	N/A	√	√	√	N/A	CPM for trisomy 13
Tufts003	XY	Declined phenotypic female	N/A	√	√	√	√	√	N/A	Vanishing twin
Tufts004	T18, XXX	46, XX	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Emergent delivery—no samples
Tufts005	MX	46, XX	√	√	√	√	√	√	N/A	Undetermined
Tufts006	M18	46, XX	√	√	√	√	√	√	N/A	Undetermined
Tufts007	XY	46, XX	N/A	√	√	√	√	√	N/A	Maternal renal transplant from brother
Tufts008	MX	46, XX	√	√	√	√	√	√	N/A	Undetermined
Tufts009	T13	46, XY	√	√	√	√	√	√	N/A	Undetermined
Tufts010	MX	46, XX	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Preterm delivery—no samples
Tufts011	Genome-wide imbalance	46, XY	√	√	√	√	√	√	√	Maternal colon cancer
Tufts012	T13	46, XX	√	√	√	√	√	√	√	Undetermined
Tufts013	M18	46, XX	√	√	√	√	√	√	√	Samples excluded

√, sample received and processed; N/A, not available.

T13, trisomy 13; MX, monosomy X; CPM, confined placental mosaicism.

Cell free DNA – Biology and Discovery

Preliminary Communication

Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies

Diana W. Bianchi, MD; Darya Chudova, PhD; Amy J. Sehnert, MD; Sucheta Bhatt, MD; Kathryn Murray, MS; Tracy L. Prosen, MD; Judy E. Garber, MD; Louise Wilkins-Haug, MD, PhD; Neeta L. Vora, MD; Stephen Warsof, MD; James Goldberg, MD; Tina Ziainia, MD; Meredith Halks-Miller, MD

Table 1. Clinical Details on the 8 Cases of Maternal Cancer That Underwent Genome-wide Analysis

	Case 1[a]	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Maternal demographics								
Age, y	37	36	33	36	23	37	39	39
GA, wk	13	12	13	20	20	12	11	10
Aneuploidy detection by NIPT								
Chromosome 21	Not detected	Not detected	Not detected	Monosomy	Trisomy	Not detected	Not detected	Trisomy
Chromosome 18	Monosomy	Monosomy	Not detected	Monosomy	Monosomy	Trisomy	Monosomy	Trisomy
Chromosome 13	Trisomy	Not detected	Trisomy	Monosomy	Trisomy	Not detected	Not detected	Trisomy
Sex chromosomes	Not done	Not done	Not done	Not done	XY	XX	XXY	Monosomy X
No. of NIPT aneuploidies	2	1	1	3	3	1	2	4
Fetal/newborn status								
Fetal karyotype	46,XY	Not done	46,XY	46,XY	46,XY	46,XX	46,XY	46,XX
Pregnancy outcome	Term male	Term female	Term male	Term male	Preterm male, preeclampsia, 29 wk	Term female	Preterm male, 35 wk	Preterm female, 32 wk
Cancer characteristics								
Cancer type	Neuro-endocrine (unknown origin)	Non-Hodgkin (B-cell) lymphoma	Colorectal	Hodgkin lymphoma	Acute T-cell lymphoblastic leukemia	Non-Hodgkin (B-cell) lymphoma	Non-Hodgkin (B-cell) lymphoma	Anal
Stage at diagnosis	IV, metastatic	IVB	IIIC	IIA	NA	IV	II	IIIB
Time elapsed from NIPT to diagnosis	28 wk	13 wk	39 wk	3 wk to MRI, 29 wk to biopsy	3 wk	≈20 wk	≈10 wk	8 wk
Timing of cancer diagnosis	Postnatal	Prenatal	Postnatal	Postnatal	Prenatal	Prenatal	Prenatal	Prenatal
Postnatal DNA sequencing results	Not done	Not done	Trisomy 13, monosomy 18	Monosomy 13, monosomy 18, monosomy 21, monosomy X	Not done	Not done	Not done	Not done

Abbreviations: GA, gestational age at time of NIPT blood draw as obtained from test request form; MRI, magnetic resonance imaging; NA, not applicable; NIPT, noninvasive prenatal testing.

The association between anticoagulation therapy, maternal characteristics, and a failed cfDNA test due to a low fetal fraction

Whitney Burns[1] | Nathanael Koelper[1,4] | Andrea Barberio[2] | M. Dy Dosia Kelly[1] | Michael Mennuti[1] | Mary D. Sammel[1,3] | Lorraine Dugoff[1]

Prenatal Diagnosis 2017;37:1125

PLoS One. 2018 Jul 12;13(7):e0200360. doi: 10.1371/journal.pone.0200360. eCollection 2018.

Maternal total cell-free DNA in preeclampsia and fetal growth restriction: Evidence of differences in maternal response to abnormal implantation.

Rafaeli-Yehudai T[1], Imterat M[1], Douvdevani A[2], Tirosh D[1], Benshalom-Tirosh N[1], Mastrolia SA[3,4], Beer-Weisel R[1], Klaitman V[1], Riff R[2], Greenbaum S[1], Alioshin A[1], Rodavsky Hanegbi G[1], Loverro G[3], Catalano MR[3], Erez O[5].

Placenta. 2014 Feb;35 Suppl:S64-8. doi: 10.1016/j.placenta.2013.11.014. Epub 2013 Dec 1.

Review: cell-free fetal DNA in the maternal circulation as an indication of placental health and disease.

Taglauer ES[1], Wilkins-Haug L[2], Bianchi DW[3].

Cf DNA – New Frontiers in Utility

< Previous Article | **April 2018** Volume 37, Issue 4, Supplement, Pages S78–S79 | Next Article >

The Journal of Heart and Lung Transplantation

Validation of Donor-derived Cell-free DNA to Detect Heart-transplant Rejection

H. Valantine[1], P. Shah[2], K. Shah[3], S. Hsu[4], E. Feller[5], M. Rodrigo[6], S. Najjar[6], U. Fideli[1], S. Gorham[1], A. Marishta[1], Y. Yang[1], M. Jang[1], I. Tunc[1], S. Agbor-Enoh[1]

J Immunol Methods. 2018 Dec;463:27-38. doi: 10.1016/j.jim.2018.09.011. Epub 2018 Sep 26.

Characteristics, properties, and potential applications of circulating cell-free dna in clinical diagnostics: a focus on transplantation.

Sherwood K[1], Weimer ET[2].

Donor-specific Cell-free DNA as a Biomarker in Solid Organ Transplantation. A Systematic Review

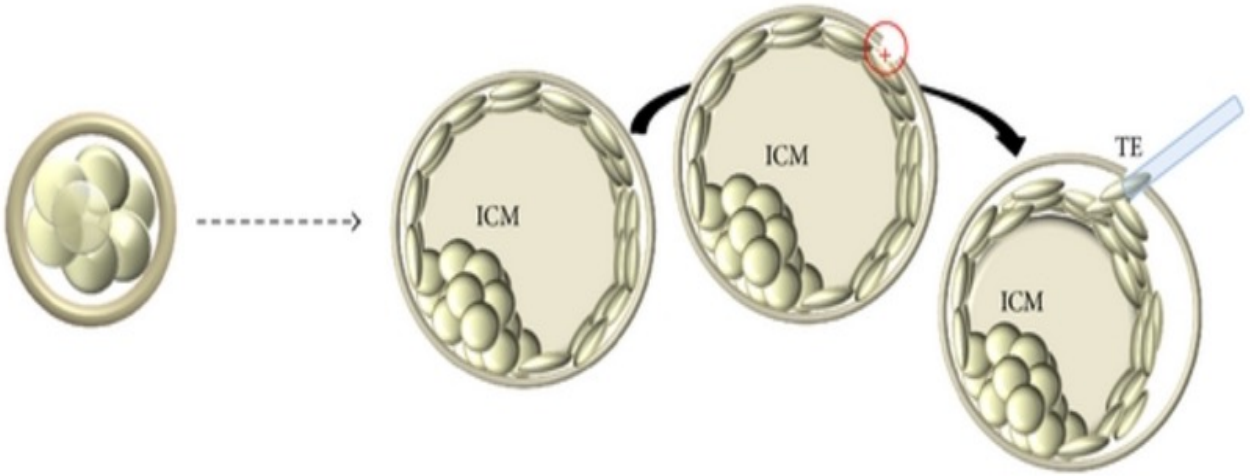
Knight, Simon Robert MChir[1,2]; Thorne, Adam BSc[1]; Lo Faro, Maria Letizia PhD[1]

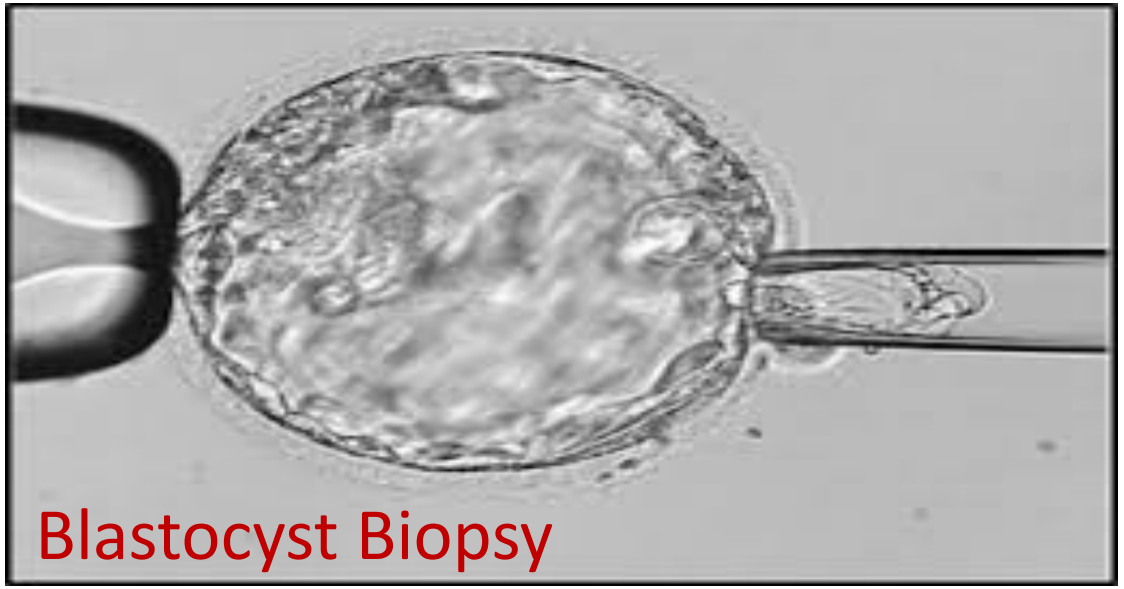
Transplantation.2019;103:273

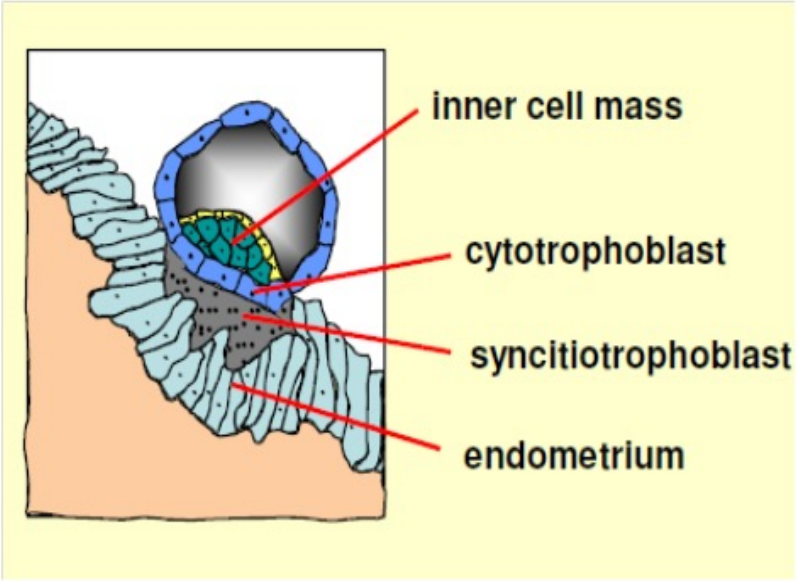
cfDNA Summary

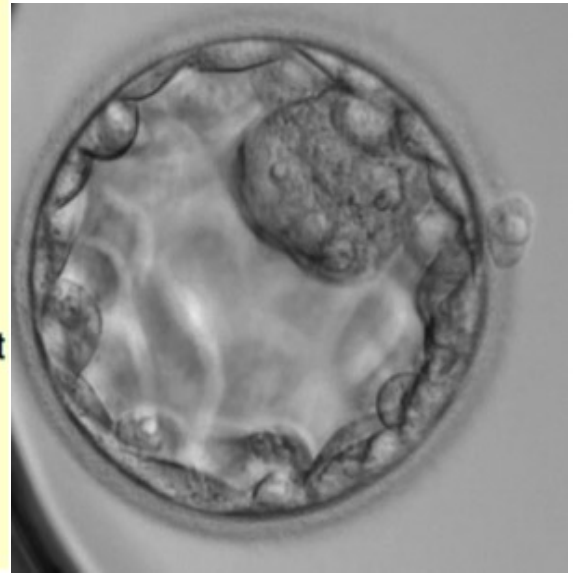
- Early diagnosis of fetal genetic conditions
  - Common aneuploidy
  - Microdeletion syndrome performance – not validated
  - Single gene – Rh Disease
  - Treatment
    - Reverse, delay, reduce severity
  - Genetic and biologic window to embryology/fetal development
  - *Risks in pregnancy – may find out more about the fetus or mother than expected*
- Early biomarker for maternal health
- Marker for fetal-maternal-environmental interactions
  - Directional alterations in trafficking
  - Biomarker for impending prenatal complications
  - Window into genetic mechanisms of fetal-maternal conversations in pregnancy
  - How does the mother and fetus make adjustments during pregnancy
- Biomarker for cancer and transplant management

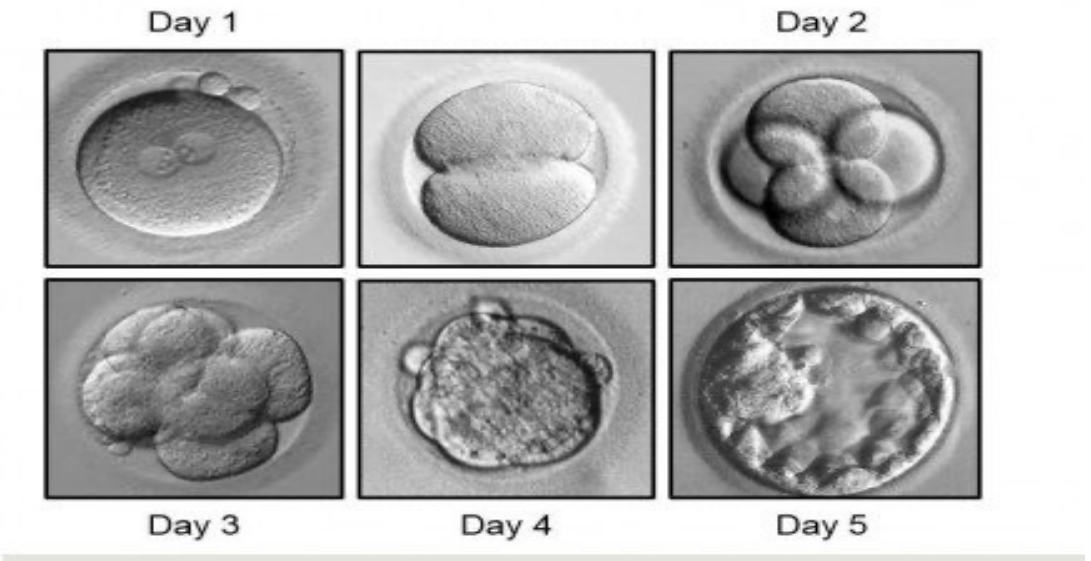
Preimplantation Genetic Diagnosis





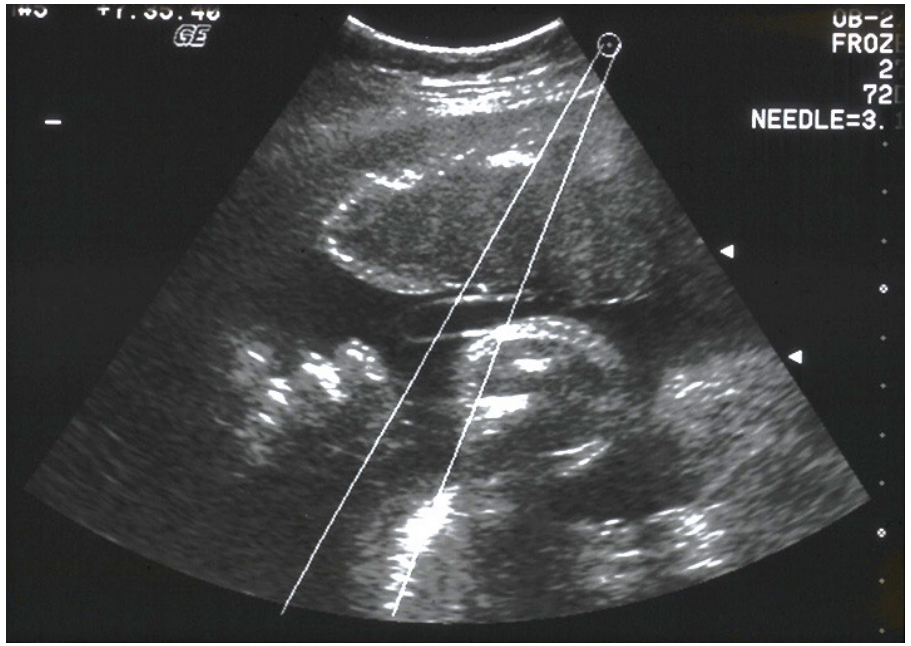






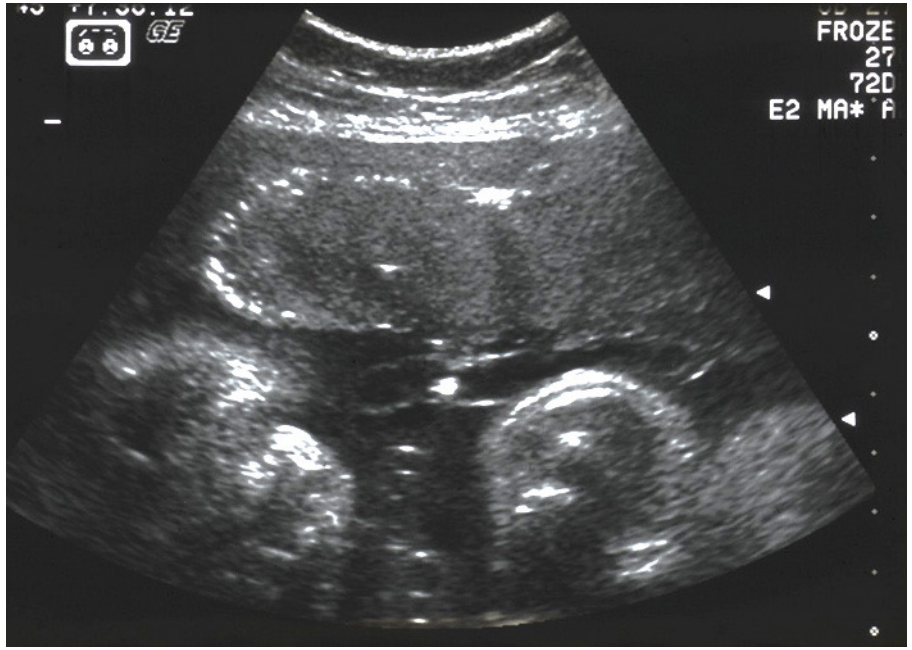
Preimplantation Genetic Testing – Lessons in human embryology

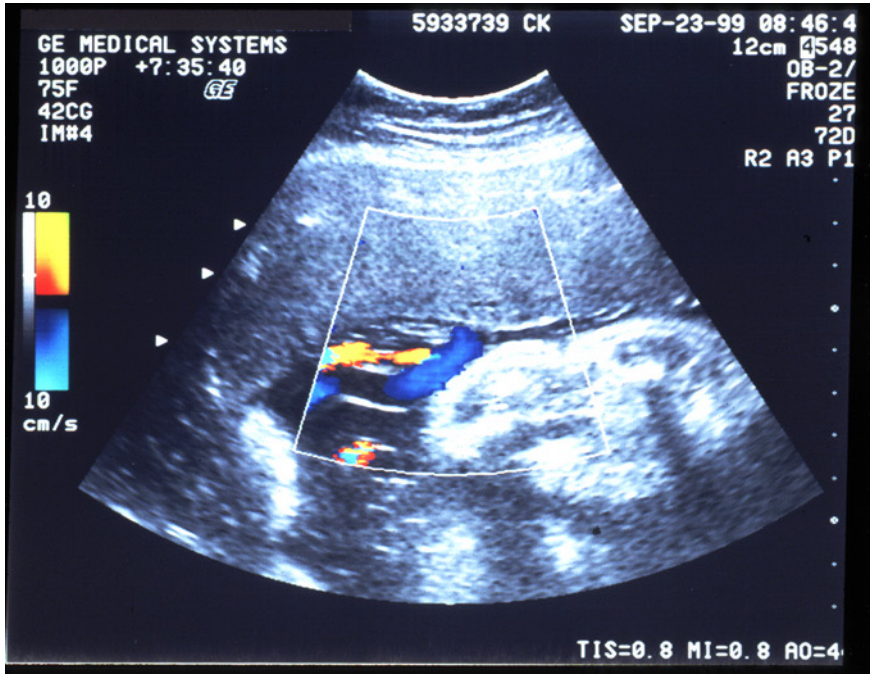
• *1990*	Intracytoplasmic Sperm Injection (ICSI)	
	Imprinting Disorder	
• *1990*	Preimplantation Genetic Diagnosis	
	Blastomere Biopsy	1 – 2 cells
	X linked disorder	PCR for Y chromosome
	Cleavage stage embryo	15 -90% mosaicism
	Meiosis I and II errors (maternal)	recombination reduction
	Aneuploidy Rescue	PGS
• *>1990*	Chorionic Villus Sampling	
	Confined Placental Mosaicism	1-2% viable pregnancies
	Trisomy Rescue	
	Uniparental Disomy Syndromes	
• *2010*	Preimplantation Genetic Screening	
	High aneuploid rate	cleavage stage
	Blastocyst stage biopsy	biopsy 5-10 cells
• *Present*	Preimplantation Genetic Testing – Aneuploidy	
	Blastocyst stage	Mosaicism –what do you transfer
• *Present*	*Embryo freezing – thawing*	*? Genetic implications*
• *Present*	*Oocyte preservation*	*? Genetic implications*



Fetal Therapy
Fetal Cordocentesis

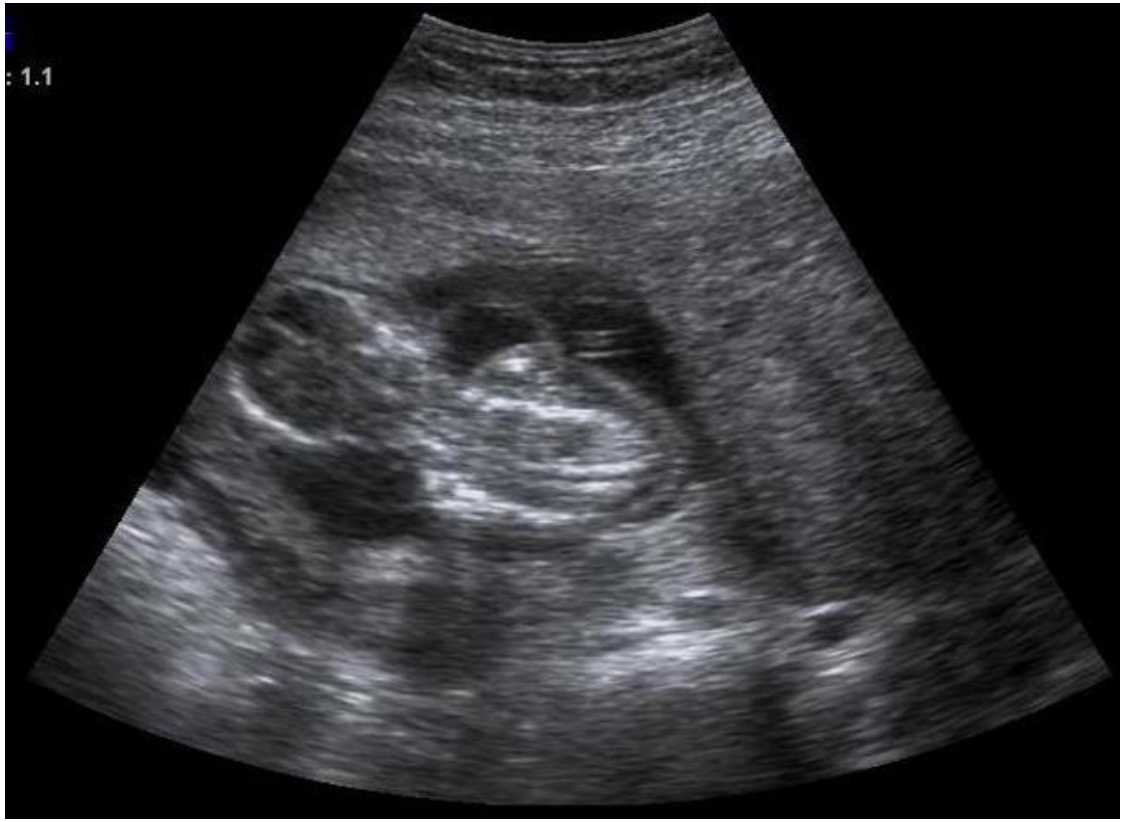
Transfusion	Fetal Anemia Fetal Thrombocytopenia
Medication	Fetal tachyarrythmia Severe fetal hypothyroid disease





Example 1 – 1st trimester increased nuchal/hydrops at 12 wks

- Cytogenomic
- Immune hydrops
  - Rh or other → unusual in 1st trimester
  - Can see in late 2nd trimester
    - Kell kills
    - RhD
- Non Immune
  - ? Parents ethnicity → alpha thalassemia
  - Severe metabolic -> storage diseases
  - Infection – Parvo is most common
  - Severe/lethal skeletal dysplasia
  - Cardiac



Mat 21 positive for T21

Amnio declined

Fetal demise at 18 wk

Final chromosome diagnosis

46,XX,der(14;21)(q10;q10), +21

Example 2 Sex chromosome aneuploidy

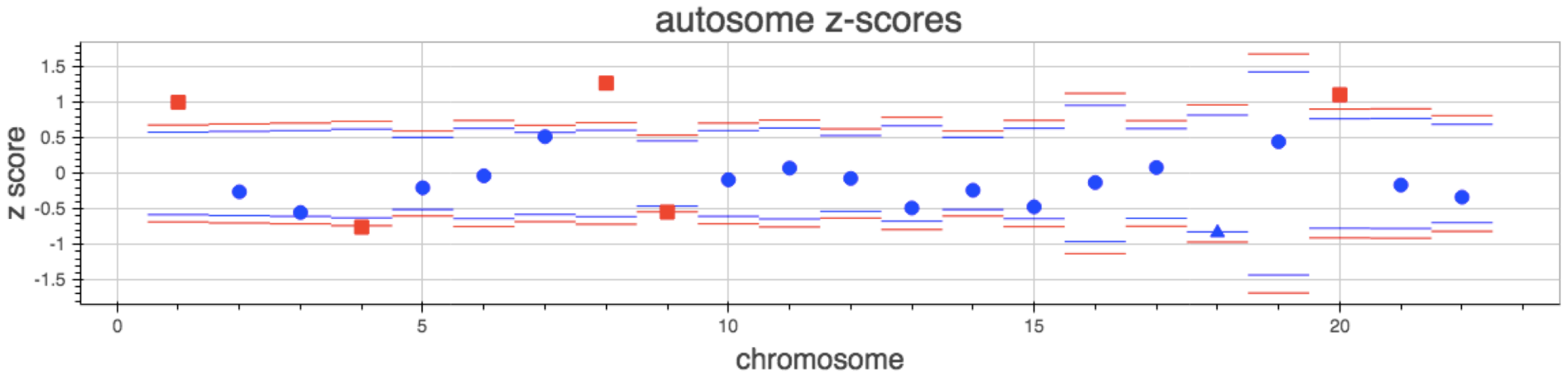
- Maternal age 41
- Normal NT
- cfDNA positive for monosomy X (Turner Syndrome)
- Maternal karyotype 45,X[5]/46, XX[45]
- Ultrasound at 16 weeks normal appears female
- Amniocentesis 46,XX in 21 clones and 100 cells from mass culture
- Ultrasound at 20 weeks detailed anatomy normal
- Reason: somatic loss of X chromosome with aging

Patient Story: 32 yo G1 Type 1 DM

11/7/18	23 - 25 wk	Ultrasound bilateral fetal pelviectasis UTD A1
		cfDNA → multiple CNVs likely maternal origin
		work-up for asymptomatic malignancy begun
1/16/19	35w3d	Severe Pre-Eclampsia with HELLP
		c/section healthy daughter
1/31/19	2 wks pp	check-up repeat cfDNA
2/19/19		pp cfDNA → multiple CNVs

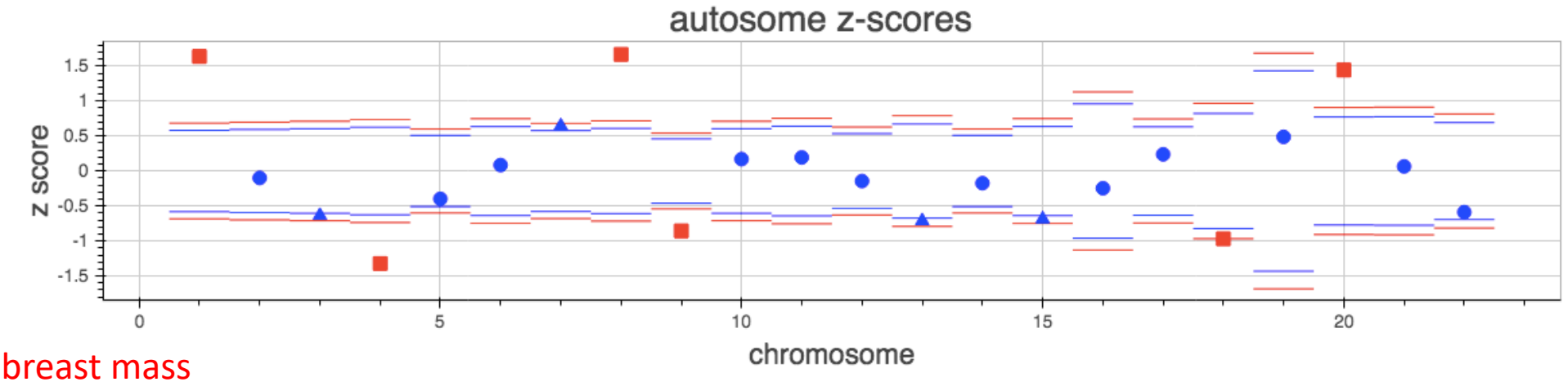
24 weeks, 3 days

Numerous whole chromosome gains and losses. Note that chromosome 17 where ERBB2/HER2 is located is within normal limits

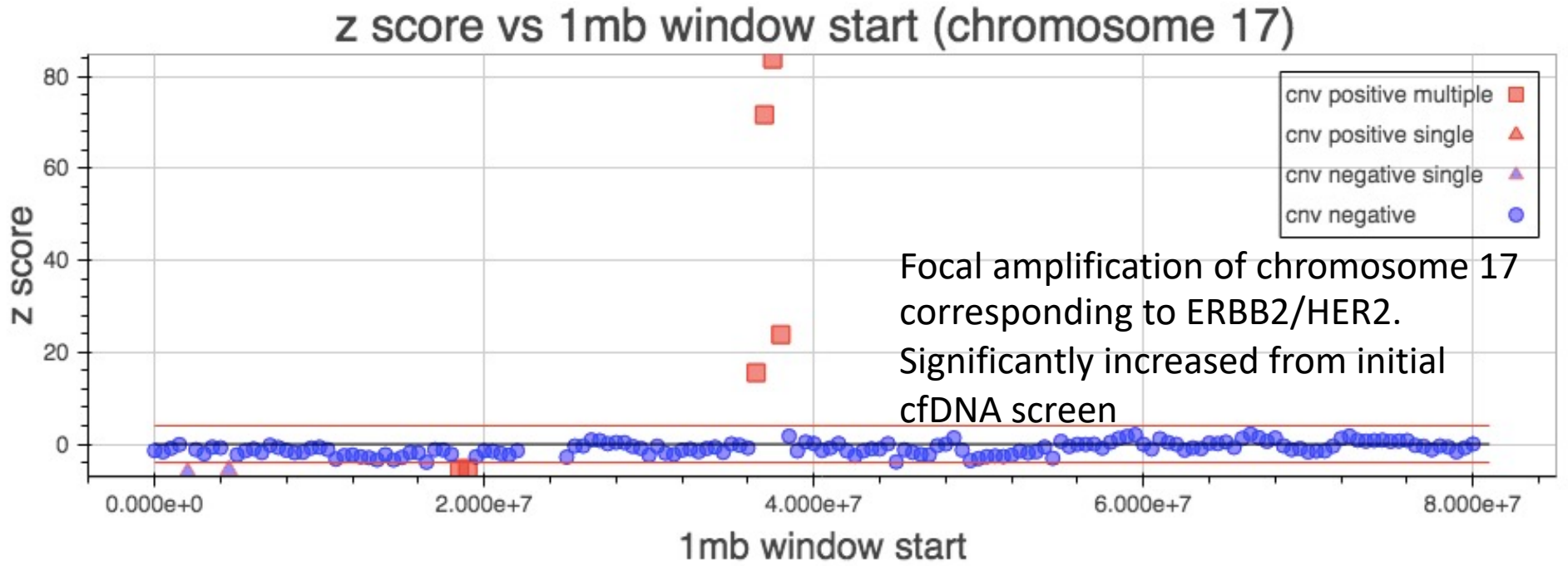


6 weeks postpartum

Numerous whole chromosome gains and losses. Note that chromosome 17 where ERBB2/HER2 is located is within normal limits



Found small breast mass



Focal amplification of chromosome 17 corresponding to ERBB2/HER2. Significantly increased from initial cfDNA screen

32 yo healthy G1

- CfDNA – commercial multiple gains and losses
- 16 wk referral to MFM
  - Large abdominal mass
  - What is your differential diagnosis

Prenatal — Adult Continuum

6q25.1 (*TAB2*) microdeletion syndrome: Congenital heart defects and cardiomyopathy

Andrew Cheng[1] | Mary Beth P. Dinulos[2] | Whitney Neufeld-Kaiser[3] | Jill Rosenfeld[4] | McKenna Kyriss[5] | Suneeta Madan-Khetarpal[6] | Hiba Risheg[7] | Peter H. Byers[3] | Yajuan J. Liu[3]

Maternal 6q25.1 microdeletion TAB 2 deleted

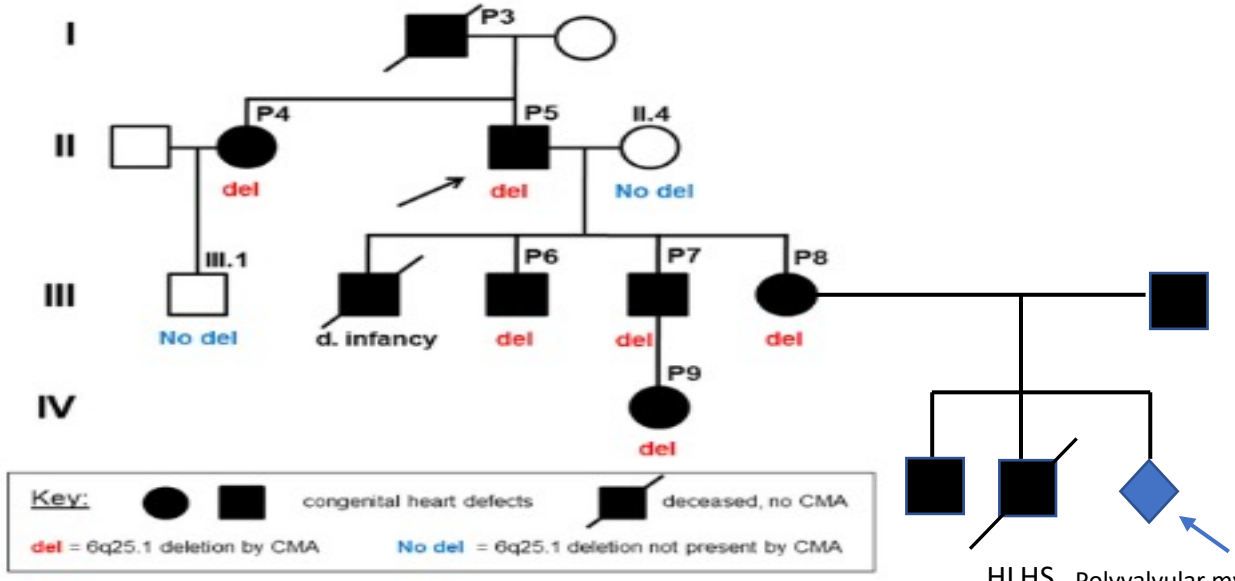


FIGURE 3 Pedigree of the four-generation family showing segregation of the 6q25.1 deletion with congenital heart defects. Circles designate females; squares designate males. CMA = cytogenomic microarray analysis. [Color figure can be viewed at wileyonlinelibrary.com]

HLHS Polyvalvular myxomatous disease
Dilated cardiomyopathy

Prenatal — Adult Continuum

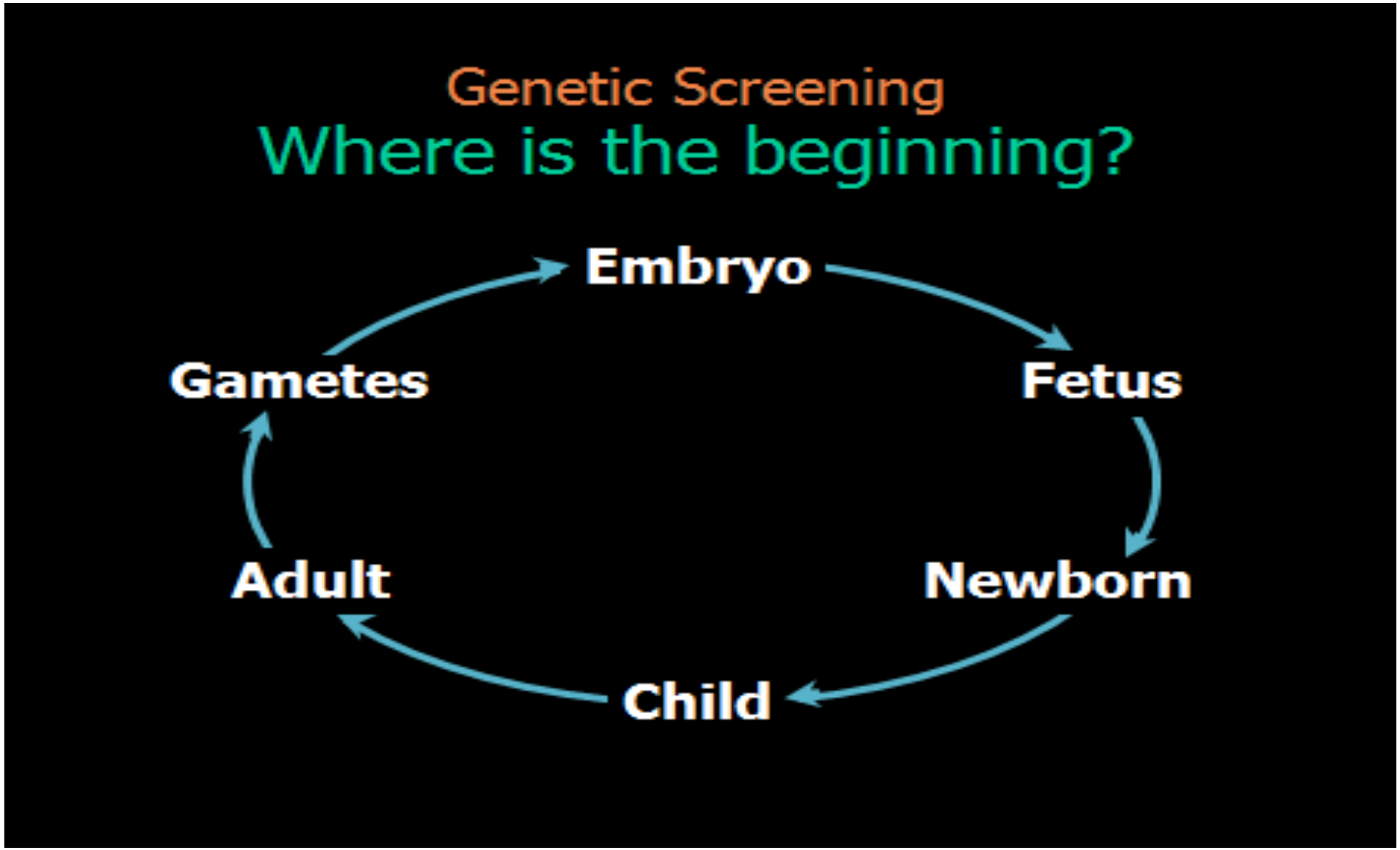
Fetal Treatment
Multidisciplinary Approach

Structural

- Twin Twin Transfusion Syndrome
- Open Neural Tube Defects
- Congenital Diaphragmatic Hernia
- Congenital Valvular Heart Disease
- Fetal Masses
- GU obstruction –shunts/laser
- Pulmonary Lesions - excision/drainage
- *EXIT (Ex-Utero Intrapartum Treatment)*

Medical

- Intrauterine Transfusion
  - Fetal anemia, thrombocytopenia
- Maternal administration
  - Betamethasone
    - Congenital Pulmonary Adenomatoid Malformations (CPAM)
  - Antiarrythmic cardiac medications
    - Fetal tachyarrythmia
- *Intra-amniotic delivery*
  - *Fetal goiter (hypothyroidism)*
  - *X-linked Hypohydrotic Ectodermal Dysplasia – Fc-EDA*
- *Intra-umbilical delivery*
  - *Stem cell transplantation (ATM)*
  - *Protein/Enzyme Replacement*


Genetic Screening
Where is the beginning?
Embryo
Fetus
Newborn
Child
Adult
Gametes