Genetic Screening: Utilization of Ultrasound and current screening practices

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Conflicts

I have no conflict of interest

Objectives

- Understand current screening test options
- Understand current recommendations and controversies with regards to cell free DNA screening
- Describe ultrasound benefit to screening options
- Review relevant clinical updates in the last year

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Comparison of Prenatal Screening

TABLE 2
Comparison of prenatal screening and diagnostic testing options for fetal aneuploidy

Test	DR T21, %	DR all aneuploidies, %	SPR, %*
First-trimester screen	80	69	5
Sequential/integrated screen	93	82	5
Cell-free DNA screen	99	72	1-9
Chorionic villus sampling	>99	>99	1[b]
Amniocentesis	>99	>99	0.2[b]

DR, detection rate; SPR, screen positive rate.

* Includes all results that required further follow up (ie, failed cell-free DNA tests and false-positive results); [b] Mosaicism, which included confined placental mosaicism.

SMFM. Prenatal aneuploidy screening with cfDNA. Am J Obstet Gynecol 2015.

Cell free DNA Screening

- The Basics
  - 10-15% of cell free DNA is placental in origin
  - Several molecular mechanisms have been developed using next generation sequencing and bioinformatics to determine fetal risk of aneuploidy
  - Screens for common trisomies and gender (SCA/microdeletions)
  - Testing can occur at 9-10 weeks
  - Results are available in 7-10 days

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Counseling Recommendations

Table 1. Key Points to Consider When Providing Pretest Counseling.*

State that testing is optional.
Clarify that this is a screening test and not a diagnostic test.
Describe limitations of the test (i.e., what it does not test for).
Review the clinical features and variability of the conditions being screened.
Briefly review test methods and reporting formats.
Define positive and negative predictive values and their clinical significance.
Recommend that all positive screening tests be confirmed with a diagnostic test to determine fetal or neonatal karyotype.
Mention the possibility of incidental findings regarding maternal health.
Refer the patient to specialists in medical genetics for unusual test results.

Bianchi DW, et al Sequencing of Circulating Cell free DNA during Pregnancy. N Engl J Med 2018;379:464-73.

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Counseling Recommendations

- Cell free DNA screening is not recommended for women with multiple gestations ☆
- Diagnostic testing should be offered rather than cell free DNA screening if a fetal structural anomaly is identified on ultrasound
- Women with an indeterminate/not reported result from cell free DNA screening should receive further counseling, ultrasound and be offered diagnostic testing
- Conventional screening are the most appropriate choice for low risk obstetric populations, although any patient may choose cell free DNA screening ☆
- Cell free DNA screen results should not be used for patient management decisions such as termination
- Routine cell free DNA screening for microdeletions should not be performed

Table 3. Test Performance.*

Trisomy	No. of Cases	cfDNA Testing	Standard Screening
		% (95% CI)	
Trisomy 21	5		
Sensitivity		100 (47.8–100)	100 (29.2–100)
Specificity		99.7 (99.3–99.9)	96.4 (95.4–97.2)
Positive predictive value		45.5 (16.7–76.6)	4.2 (0.9–11.7)
Negative predictive value		100 (99.8–100)	100 (99.8–100)
Trisomy 18	2		
Sensitivity		100 (15.8–100)	100 (2.5–100)
Specificity		99.8 (99.6–100)	99.4 (99.0–99.7)
Positive predictive value		40.0 (5.3–85.3)	8.3 (0.2–38.5)
Negative predictive value		100 (99.8–100)	100 (99.8–100)

* Included in the test performance analysis for standard screening were 1912 patients who were tested for trisomy 21 (1909 unaffected patients plus 3 with true positivity) and 1906 patients who were tested for trisomy 18 (1905 unaffected patients plus 1 with true positivity). For the cfDNA test performance, results from standard screening were not required. Test analysis for cfDNA included 1952 patients who were tested for trisomy 21 (1947 unaffected patients plus 5 with true positivity) and 1952 patients who were tested for trisomy 18 (1950 unaffected patients plus 2 with true positivity).

Bianchi DW, et al. NEJM 2014;370:799-808.

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Age based PPV

Table 1. Cell-free DNA Test Performance Characteristics in Patients Who Receive an Interpretable Result*

	Sensitivity (%)	Specificity (%)	Age 25 years PPV (%)	Age 40 years PPV (%)
Trisomy 21	99.3	99.8	33	87
Trisomy 18	97.4	99.8	13	68
Trisomy 13	91.6	99.9	9	57
Sex chromosome aneuploidy	91.0	99.6	...†	...

ACOG/SMFM Committee Opinion #640 September 2015

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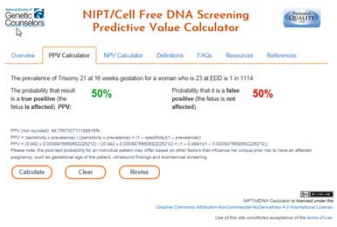
PPV for 23 year old with NIPT positive for Trisomy 21



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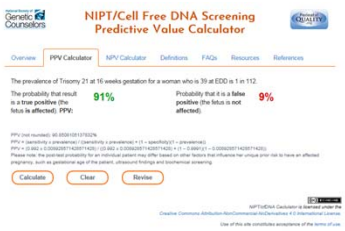
PPV for 39 year old with NIPT positive for Trisomy 21



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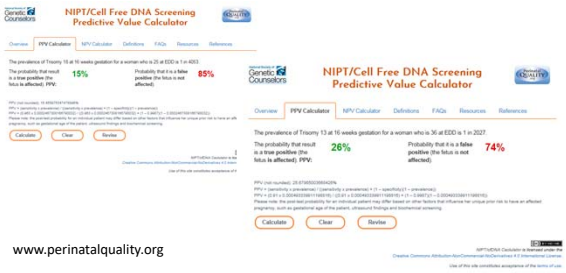

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Chromosome abnormalities identified

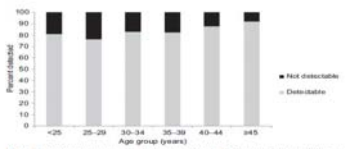


Fig. 1. Percentage of chromosomal defects detectable or not detectable by noninvasive prenatal testing based on maternal age. For numeric details, see Table 4. *Norton. Aneuploidies and Nonvasive Prenatal Testing. Obstet Gynecol 2014.*

Clinical experience-important points

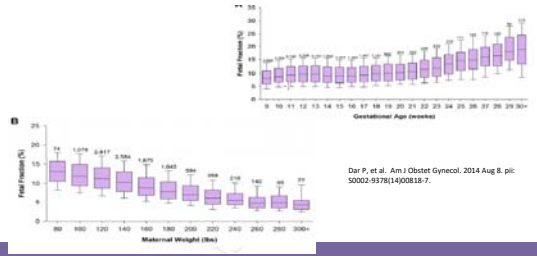
- Clinical experience from Einstein/Natera 3/13-9/13 with outcome data in 17,885 women
  - 356/17,885 High risk results (1.8%)
    - 184 (51.7%) True Positive
    - 38 (10.7%) False Positive
    - 19 (5.3%) US finding suggestive of aneuploidy
    - 36 (10.1%) SAB-no karyotype
    - 22 (6.2%) termination-no karyotype
    - 57 (16%) lost to follow up

Dar P, et al. Am J Obstet Gynecol. 2014 Aug 8.

Fetal Fraction

- The amount of cell free DNA in maternal blood which is fetal in origin
- 4% cutoff for some labs
- Risk factor for screen failure
- Low fetal fraction associated with
  - Aneuploidy (2.7% Norton NEJM 2015)
  - Maternal Obesity (Norton NEJM 2015, Dar AJOG 2014, Kinnings Prenatal Diagnosis 2015)

Fetal Fraction



Dar P, et al. Am J Obstet Gynecol. 2014 Aug 8. pii: S0002-9378(14)00818-7.

Cell Free DNA Screening in Twins

- Not recommended by ACOG/SMFM
- Limited Data

Huang X et al. Prenatal Diagnosis 2014;34:335-40

  - 189 women with twins cell free DNA screening was compared with kartyotype
    - 9/9 Trisomy 21 detected
    - 1/2 Trisomy 18 detected*

Bevilacqua E, et al Ultrasound Obstet Gynecol 2015;45(1)61-6; Nicolaides et al Ultrasound Obstet Gynecol Mar 2016 epub

  - Recent studies note higher failure rate in twins (5.4% vs 1.7%) and lower fetal fractions (8.7% vs 11.7%)

Tan Y, et al Prenatal Dx 2016:36 July

  - 565 women with twins NIPT with failure in 5; 4 T21 positive, no FN

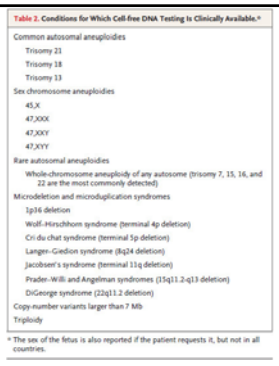


Table 2. Conditions for Which Cell-free DNA Testing Is Clinically Available.*

Common autosomal aneuploidies
Trisomy 21
Trisomy 18
Trisomy 13
Sex chromosome aneuploidies
45,X
47,XXX
47,XXY
47,XYY
Rare autosomal aneuploidies
Whole-chromosome aneuploidy of any autosome (trisomy 7, 15, 16, and 22 are the most commonly detected)
Microdeletion and microduplication syndromes
1p36 deletion
Wolf–Hirschhorn syndrome (terminal 4p deletion)
Cri du chat syndrome (terminal 5p deletion)
Langer–Giedion syndrome (8q24 deletion)
Jacobsen's syndrome (terminal 11q deletion)
Prader–Willi and Angelman syndromes (15q11.2-q13 deletion)
DiGeorge syndrome (22q11.2 deletion)
Copy-number variants larger than 7 Mb
Triploidy

* The sex of the fetus is also reported if the patient requests it, but not in all countries.

Bianchi DW, et al Sequencing of Circulating Cell free DNA during Pregnancy. N Engl J Med 2018;379:464-73.

Sex chromosome aneuploidy and gender testing

- Gender discordance has been identified due to co-twin demise, transplantation and ambiguous genitalia
- Sex chromosome aneuploidy is common 1/400-500 live births; Monosomy X occurs >1/100 gestations.
- Sensitivity 96%, FP 0.3%, non-reportable rate 5% (Mazloom AR, et al Prenatal Diagnosis 2013)
- PPV 39% (ACOG Screening for fetal aneuploidy2018)

Microdeletions

- Microdeletion occur sporadically 1/60 (Wapner NEJM 2012)
- Not clinically validated
- Not recommended by ACOG/SMFM
- Low PPV

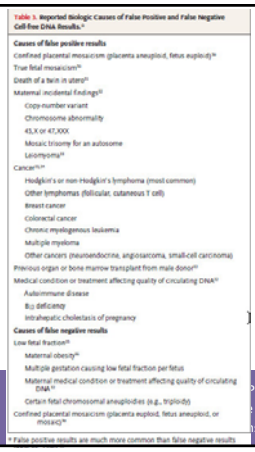


Table 3. Reported Biologic Causes of False Positive and False Negative Cell-free DNA Results.*

Causes of false positive results
Confined placental mosaicism (placenta aneuploid, fetus euploid)[36]
True fetal mosaicism[36]
Death of a twin in utero[36]
Maternal incidental findings[36]
Copy-number variant
Chromosome abnormality
45,X or 47,XXX
Mosaic trisomy for an autosome
Leiomyoma[36]
Cancer[36,39]
Hodgkin's or non-Hodgkin's lymphoma (most common)
Other lymphomas (follicular, cutaneous T cell)
Breast cancer
Colorectal cancer
Chronic myelogenous leukemia
Multiple myeloma
Other cancers (neuroendocrine, angiosarcoma, small-cell carcinoma)
Previous organ or bone marrow transplant from male donor[40]
Medical condition or treatment affecting quality of circulating DNA[41]
Autoimmune disease
B-D deficiency
Intrahepatic cholestasis of pregnancy
Causes of false negative results
Low fetal fraction[36]
Maternal obesity[42]
Multiple gestation causing low fetal fraction per fetus
Maternal medical condition or treatment affecting quality of circulating DNA[41]
Certain fetal chromosomal aneuploidies (e.g., triploidy)
Confined placental mosaicism (placenta euploid, fetus aneuploid, or mosaic)[36]

* False positive results are much more common than false negative results

Controversy

- Low risk women
  - ACMG suggests giving patients autonomy to choose genetic screening or testing options after counseling
  - Increased risk for chromosome abnormality that cannot be detected by standard NIPT in young women
- Multiples
  - Lower sensitivity of all screening modalities
  - ACOG/SMFM does not recommend NIPT in multiples-newer studies suggest reasonable performance
- Retesting after no result
  - More data coming out with algorithms for who to retest based on gestational age and fetal fraction

NIPT after abnormal serum screen

- May delay results
- California prenatal screening program evaluated traditional screen detection with NIPT and noted
  - NIPT may fail to identify some aneuploidy-2%

Norton, ME et al Ob Gyn 2014;124:979-84.

NIPT after no result

- Increased risk for aneuploidy in no call samples
  - Risk as high as 23%
    - Highest risk with low fetal fraction<1.5%
    - Risk for Triploidy in the group-know your testing

Pergament E, et al Ob Gyn 2014;124:210-8.

Controversy

- Ultrasound with NIPT
  - Prior to NIPT for dating, ruling out twins gestation and ruling out early pregnancy loss
  - Small change in detection of chromosome abnormality with large increase in recommendation for CVS

TABLE 1
Detection rate of significant chromosomal abnormalities in a high-risk cohort[a] referred for first-trimester diagnostic testing: comparison of cfDNA only with cfDNA plus NT and diagnostic testing for those above a NT threshold

Variable	cfDNA only	cfDNA plus NT; CVS for NT ≥3.0 mm
Detection rate of all chromosomal abnormalities	88.9%	94.8%
Screen-positive/CVS rate	2.0%	21.7%
Residual risk of significant chromosome abnormality	2.5%	1.00%

cfDNA, cell-free DNA screening; CVS, chorionic villus sampling; NT, nuchal translucency.
[a] High risk is defined as any of the following: increased NT with or without biochemistry, structural anomalies, advanced maternal age/elderly, or family history.
Data from Khalil et al.[1]
Society for Maternal-Fetal Medicine. Ultrasound and cell-free DNA screening. Am J Obstet Gynecol 2015.

NIPT after abnormal ultrasound

- 290 women with fetal anomaly underwent NIPT
- 29 had abnormalities not detected by standard NIPT
  - 13 were sex chromosome abnormalities now typically identified by NIPT (still leaves 5.5% undetected) Benachi, A, et al. Ob Gyn 2015;125:1330-37.
- Wapner prenatal diagnosis study of chromosome microarray versus karyotype identified 552 chromosome abnormalities
  - 178 could not be detected by NIPT (32%) Wapner, RJ, et al NEJM 2012;267:2175-84.

Malignancy and NIPT

Table 2. Association of Maternal Cancers With Different Types of Aneuploidies Detected at Noninvasive Prenatal Testing

Type of Aneuploidy Detected by NIPT	Total No. of Samples	No. of Known Maternal Cancers (%) [95% CI]
Single trisomy[a]	2650	2 (0.08) [0-0.27]
Single SCA[b]	950	0 (0) [0-0.39]
Single trisomy + SCA	30	0 (0) [0-11.5]
Single monosomy	88	1 (1.14) [0-6.1]
Multiple aneuploidy[c]	39	7 (17.9) [7.5-33.5]
Total abnormal NIPT	3757	10 (0.26) [0.12-0.48]

Abbreviations: NIPT, noninvasive prenatal testing; SCA, sex chromosome abnormality.
[a] Single trisomy refers specifically to trisomy of chromosomes 13, 18, or 21.
[b] Single SCA refers to the presence of 1 of the sex chromosome aneuploidies: Turner syndrome (monosomy X), Klinefelter syndrome (XXY), XYY syndrome, or trisomy X (XXX).
[c] The multiple aneuploidy category includes every other combination of autosomal and/or sex chromosome aneuploidy except single trisomy and SCA as noted in the Table.

Bianchi DW, et al. JAMA 2015. 314(2):162-69.

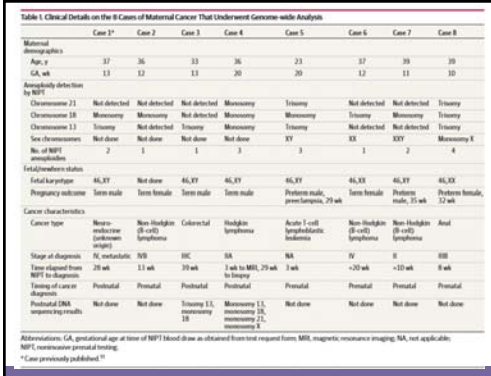


Table 1. Clinical Details on the 8 Cases of Maternal Cancer That Underwent Genome-wide Analysis

	Case 1*	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	Neuroendocrine (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.
* Case previously published.[11]

Bianchi DW, et al. JAMA 2015. 314(2):162-69.

2019 Updates: TWINS

- Twin validation study of SNP based NIPT platform
  - Zygosity, aneuploidy, fetal sex

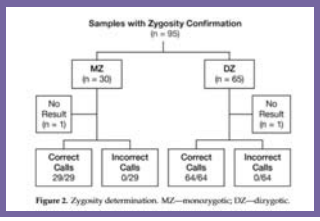


Figure 2. Zygosity determination. MZ—monozygotic; DZ—dizygotic.

2.1% No call Rate

Norwitz ER, et al. Validation of a single nucleotide polymorphism based non-invasive prenatal test in twin gestations: Determination of zygosity, individual fetal sex and aneuploidy. J Clin Med 2019, 8, 937.

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2019 Updates: TWINS

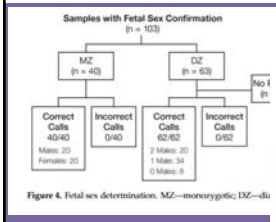

Figure 4. Fetal sex determination. MZ—monozygotic; DZ—di

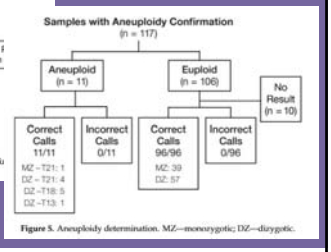

Figure 5. Aneuploidy determination. MZ—monozygotic; DZ—dizygotic.

Norwitz ER, et al. Validation of a single nucleotide polymorphism based non-invasive prenatal test in twin gestations: Determination of zygosity, individual fetal sex and aneuploidy. J Clin Med 2019, 8, 937.

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2019 Updates: TWINS

- Accurate determination of zygosity is beneficial when chorionicity is uncertain. Provides information for prognosis and management plan for pregnancy.
- Aneuploidy screening provides alternative genetic screening options in twin pregnancy.

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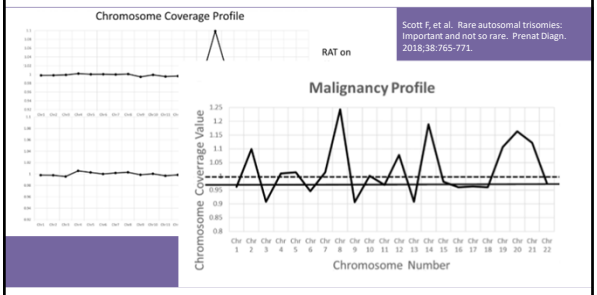
2019 Updates: Rare Autosomal Trisomies



Scott F, et al. Rare autosomal trisomies: Important and not so rare. Prenat Diagn. 2018;38:765-771.

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2019 Updates: Rare Autosomal Trisomies

TABLE 1 Clinical outcome data for each RAT case

	N	Missed or Early Misc.	TFM	U/S Anomaly	TOP	IUGR	Prem	LB
Trisomy 2	1					1	1	1
Trisomy 3	1							1
Trisomy 4	3					2	2	3
Trisomy 5	1			1		1		1
Trisomy 7	6			1	1	2		5
Trisomy 8	2							2
Trisomy 9	1	1						
Trisomy 10	1			1	1			
Trisomy 14	2	1		1		1		1
Trisomy 15	2	1	1		1			
Trisomy 16	4		1	2	1	2	2	3
Trisomy 20	1							1
Trisomy 22	3	3						
Total	28	6	2	6	4	9	5	18

Some cases are included in multiple fields eg, can have an ultrasound anomaly and true fetal mosaicism.
Abbreviations: IUGR, intrauterine growth restriction; LB, live birth; Misc., miscarriage; Prem, premature delivery; TFM, true fetal mosaic; TOP, termination of pregnancy; U/S anomaly, ultrasound anomaly seen.

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2019 Updates: Women's screening choices

- 7939 women with first t
  study
  - 352 were high risk fo
    - 291 opted for NI
    - 52 opted for inva
    - 5 women opted f
    - 3 women opted f
    - 1 woman was dia

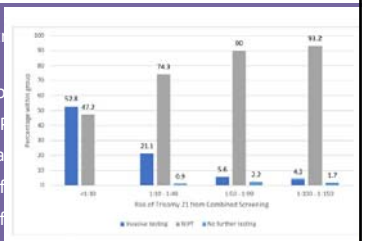

Figure 2 Choices made regarding further testing according to level of chance from combined screening, NIPT, non-invasive prenatal testing.

Sacco A, et al. Women's choices in non-invasive prenatal testing for aneuploidy screening: results from a single centre prior to introduction in England. Arch Dis Child 2019;0:1-6.

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2019 Updates: Women's screening choices

- Important to note the high rate of NIPT following abnormal first screen
  - May be missing what we are not screening for
- High rate of subsequent testing after first screen compared to populations I have worked with in the past.

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2019 Updates: Impact of NIPT on invasive testing

- 500 cases of CNS anomalies were reviewed from 2010-2017
  - 33% (165) Expectant management
  - 33% (166) invasive testing
  - 10% (52) NIPT
  - 23% (117) Termination
- Increase from no testing with NIPT
- No change in invasive testing

Al Toukhi S, et al. Impact of NIPT on testing in CNS anomalies. Prenatl Diagn 2019;June 39 (7)544-48.

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2019 Updates: Impact of NIPT on invasive testing

- NIPT missed 4% CNV in isolated brain malformation
- NIPT missed 11% CNV in complex brain/other malformation
- NIPT and invasive testing are not equivalent

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2019 Updates: Role of ultrasound

- High risk NIPT for T18/13
  - >90% (32/35) with true T18/13 had fetal abnormality on ultrasound
  - No ultrasound abnormality when confined placental mosaicism or normal amniocentesis

Zhen L, et al. Role of Ultrasound in NIPT T18/13. Pren Diag. 2019; July 12. epub.

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2019 Updates: Sex Chromosome Aneuploidy Screening

TABLE 3 Percent* of pediatric genetic counselors who always offer a specific option by scenario

	X,Y FISH	Karyotype	CMA	Ultrasound (pelvic/renal/abdominal)	Maternal karyotype	Echocardiogram	Other
Scenario 1: Newborn with NIPT positive for 45,X with webbed neck and puffy hands							
Initial appointment	52.2	84.9	32.0	50.0	5.8	70.0	50.0
Normal 46,XX karyotype	16.7		28.4	37.5	28.6	52.4	33.3
Scenario 2: Newborn with NIPT positive for 45,X and no physical findings							
Initial appointment	64.3	73.1	28.6	36.4	28.6	52.9	100.0
Scenario 3: Newborn with NIPT positive for 47,XXX							
Initial appointment	77.8	85.2	41.7		30.0		0.0
Normal 46,XX karyotype	14.3		27.3		46.2		No responses
Scenario 4: Newborn with NIPT positive for 47,XYY							
Initial appointment	63.6	84.6	50.0		33.3		No responses
Normal 46,XX karyotype	60.0		30.8		33.3		No responses

Note. CMA: chromosomal microarray; NIPT: non invasive prenatal testing.
*Percent is based on number of respondents for a specific scenario who indicated they Always offer a certain option (diagnostic testing, specialty imaging, or referral) based on a five point likert scale from Never to Always.

Fleddermann L, et al. Current genetic counseling practice in the US following positive non-invasive prenatal testing for sex chromosome abnormalities. J Genet Counseling 2019; 28-802-811

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2019 Updates: The Future

- Plasma DNA tissue mapping
- IDENTIFY study-Diana Bianchi NICHD
- Trisomy 21 in utero treatment trial-Apigenin
- Fetal treatment trials-in utero human stem cell transplantation for alpha thalassemia

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Thank you!

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