Prenatal test for Down Syndrome Screening

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Conflict of Interest and Disclaimers

The opinions and content presented are the professional views of Farid Hadi, MD and do not necessarily reflect the opinion of his employer.

Harmony is a non-invasive prenatal test (NIPT) based on cell-free DNA analysis and is considered a prenatal screening test, not a diagnostic test. Harmony does not screen for potential chromosomal or genetic conditions other than those expressly identified in this document. Before making any treatment decisions, all women should discuss their results with their healthcare provider, who can recommend confirmatory, diagnostic testing where appropriate.

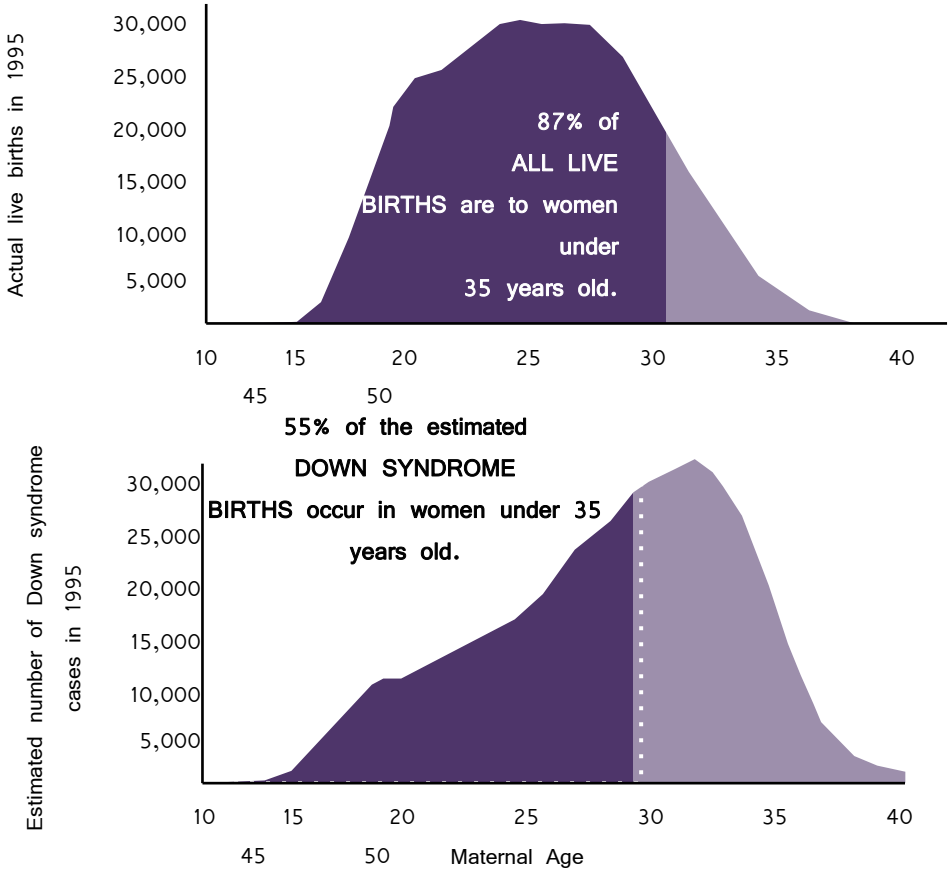
The Harmony Prenatal Test was developed, and its performance characteristics determined by Ariosa Diagnostics, a CLIA and CAP accredited clinical laboratory in San Jose, CA USA. This testing service has not been cleared or approved by the US FDA.

DESPERATE HOUSEWIVES

Eva's heroes

interact • grow • learn • love

Importance of prenatal screening in women of any age



Majority of babies born with Down syndrome are in women under 35 years old

Effective screening strategy is required for **all** pregnant women

The California Prenatal Screening Program. March 2009. *Provider Handbook 2009.* Retrieved from www.cdph.ca.gov/programs/pns

Professional Society Guidelines

Who to screen for Down Syndrome?

- **Candidates for prenatal screening:**
  - All women should be offered aneuploidy screening before 20 weeks gestation
  - All women should have the option of invasive testing, regardless of age
- **Candidates for prenatal diagnosis:**
  - Previous pregnancy complicated by foetal trisomy
  - At least one major or two minor fetal structural anomalies in the current pregnancy
  - Chromosomal translocation, inversion or aneuploidy in the pregnant women or her partner

American College of Obstetricians and Gynecologists. Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologist. Number 163, May 2016.

Prenatal Trisomy Test Modalities

Invasive test - amniocentesis

- 1st trimester: Chorionic villus sampling (CVS)
  - Obtain tissue/cells from placenta
  - **0.5 – 2% risk of miscarriage**, infections and amniotic leakage
- 2nd trimester: Amniocentesis (safer than CVS)
  - Obtain tissue/cells from fetus (through amniotic fluid
  - **0.3 – 1% risk of miscarriage** and amniotic leakage
- Cordocentesis
  - Percutaneous umbilical blood sampling (PUBS) from umbilical vein
  - **1 – 2% risk of miscarriage**

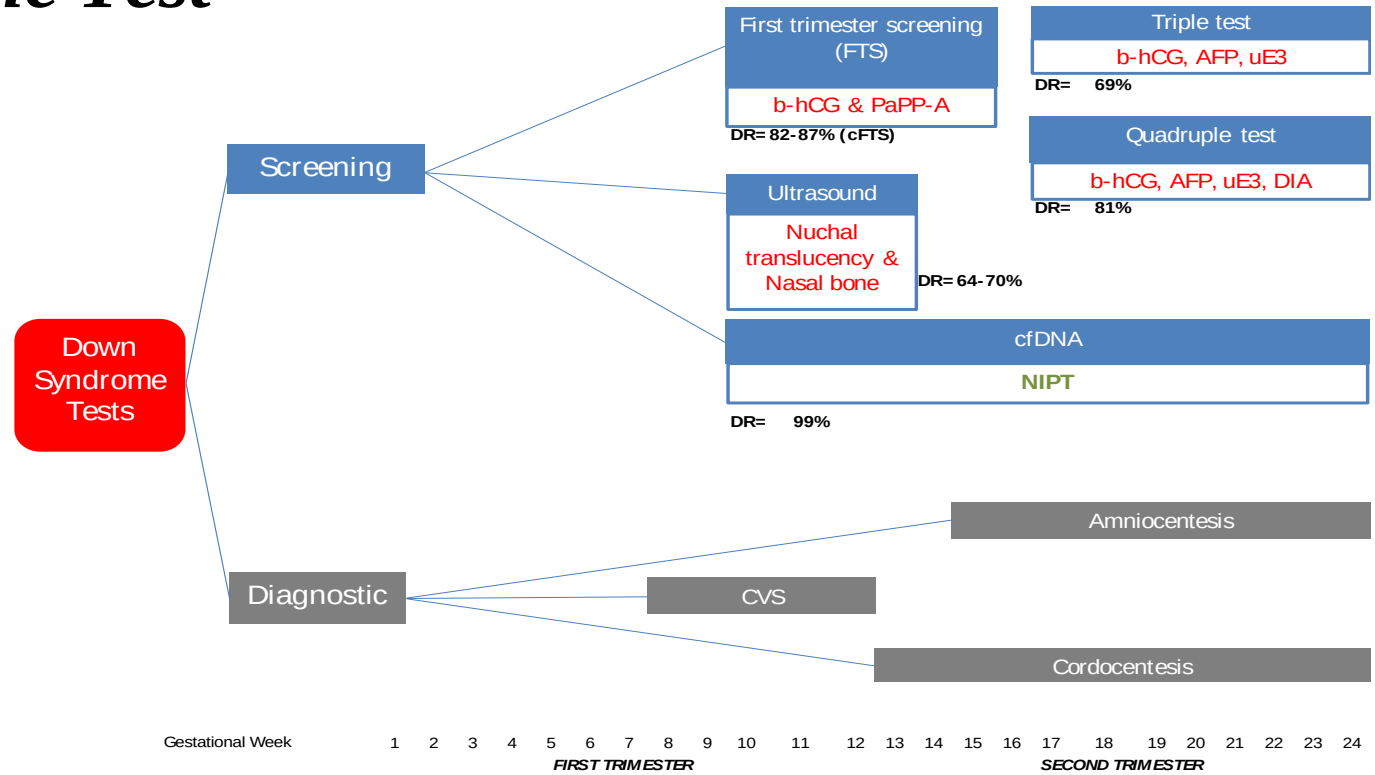
All samples are karyotyped by PCR or FISH

Sensitivity/specificity ≥99%

Approx 1% risk of miscarriage

Prenatal Trisomy Test Modalities

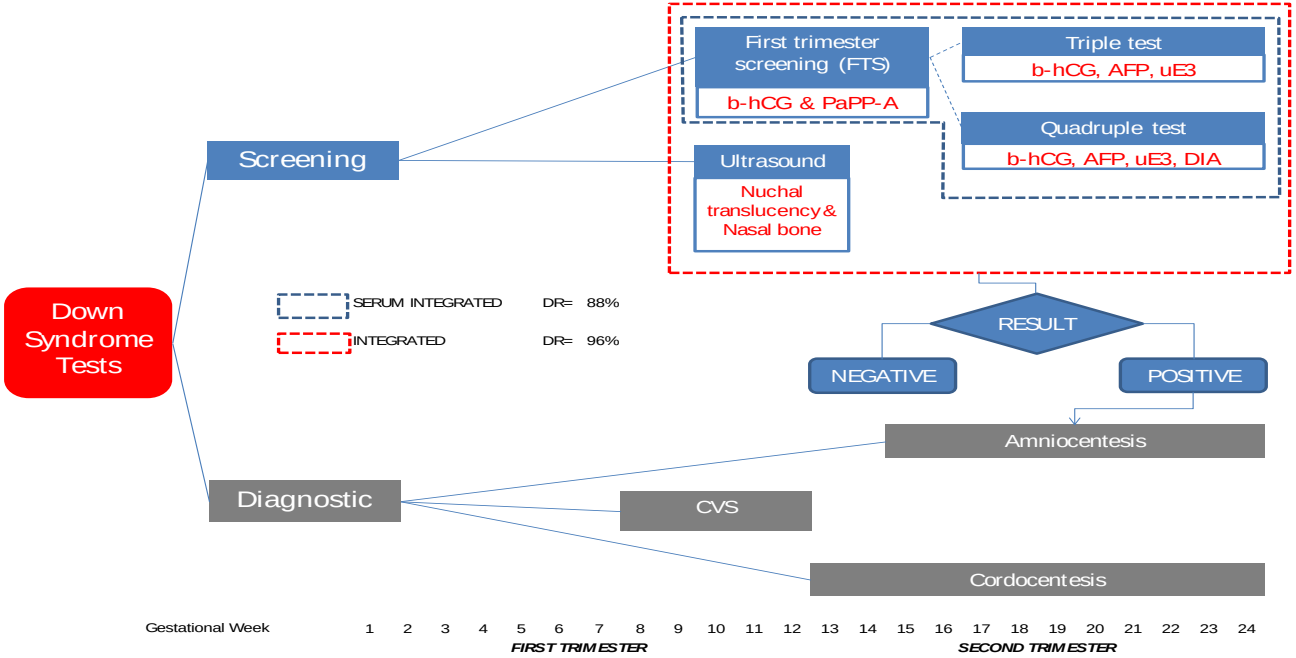
Single Test



American College of Obstetricians and Gynecologists. Practice Bulletin. Clinical Management Guidelines for Obstetrician–Gynecologist. Number 163, May 2016.

Prenatal Trisomy Test Modalities

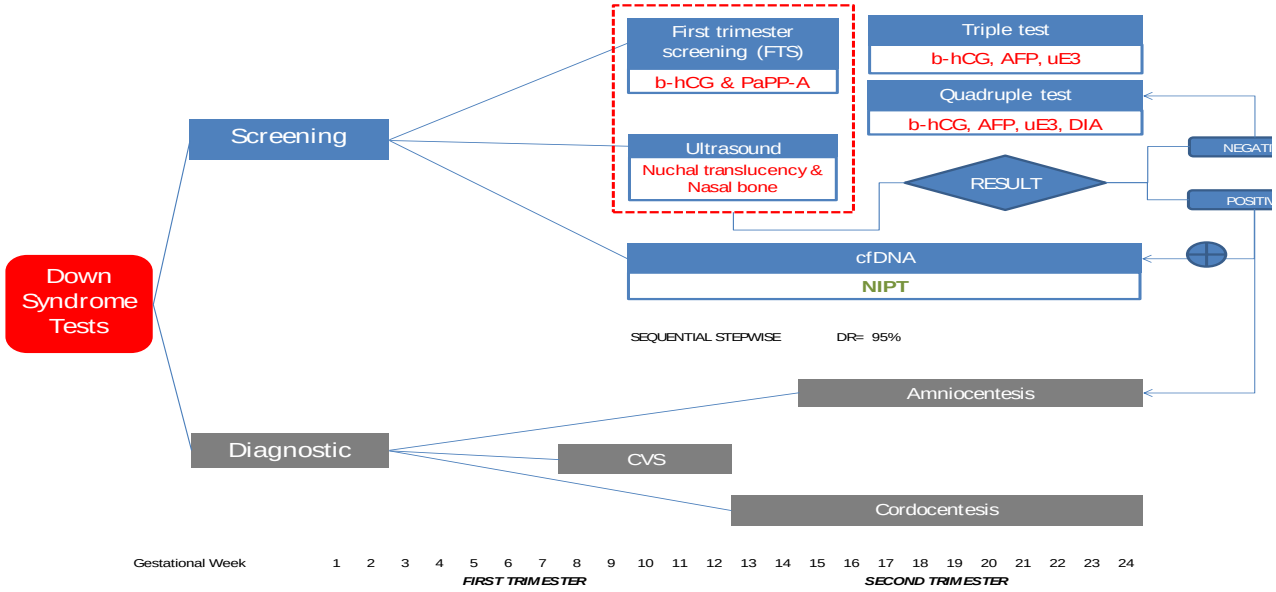
Combined Integrated Tests



American College of Obstetricians and Gynecologists. Practice Bulletin. Clinical Management Guidelines for Obstetrician–Gynecologist. Number 163, May 2016.

Prenatal Trisomy Test Modalities

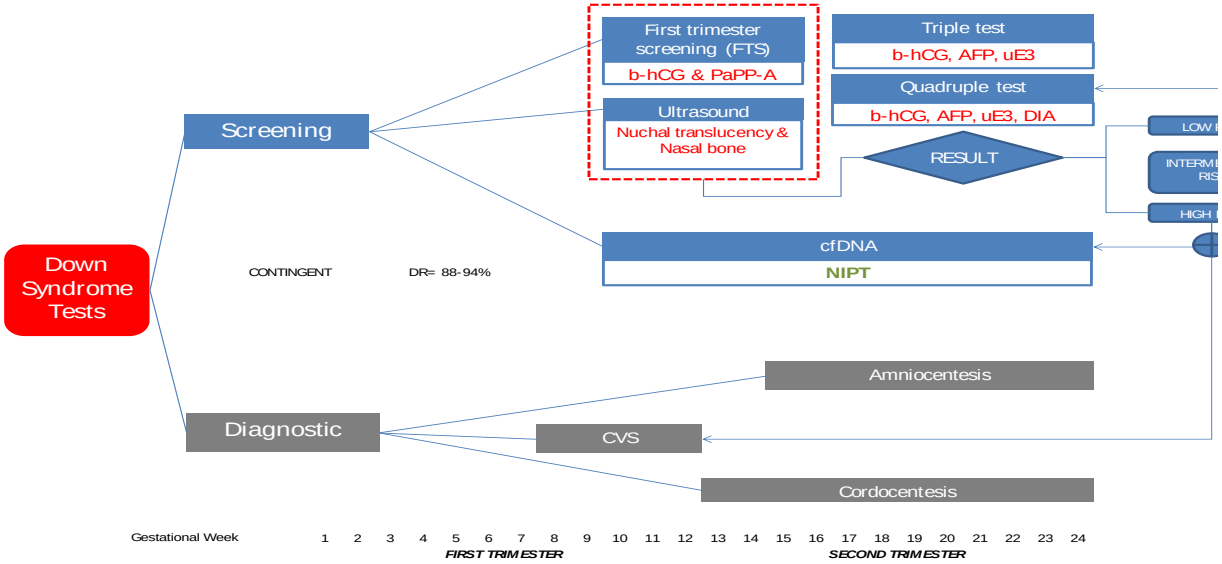
Combined Stepwise Tests



American College of Obstetricians and Gynecologists. Practice Bulletin. Clinical Management Guidelines for Obstetrician–Gynecologist. Number 163, May 2016.

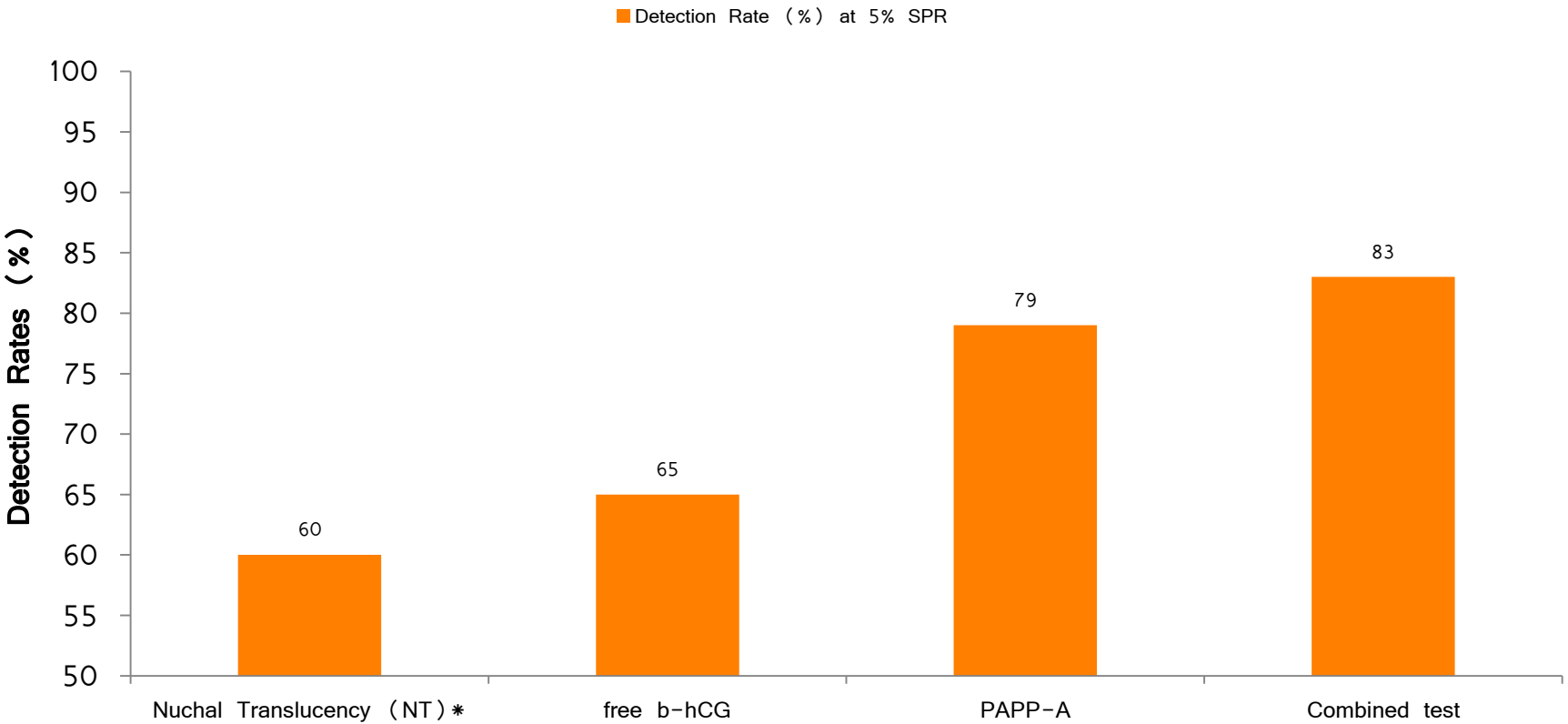
Prenatal Trisomy Test Modalities

Combined Contingency Tests



American College of Obstetricians and Gynecologists. Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologist. Number 163, May 2016.

Biomarkers in First Trimesters

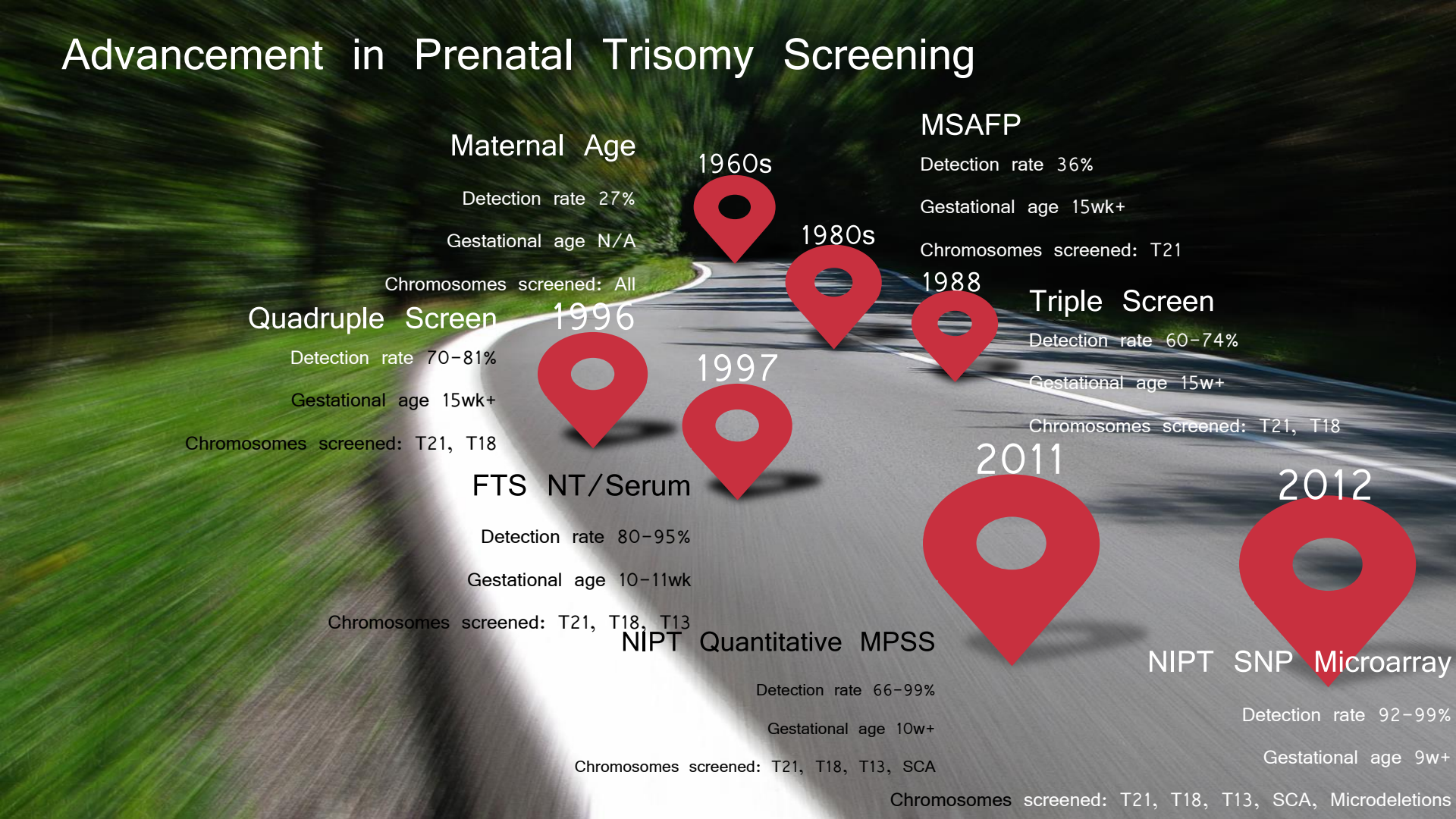


*) 10–13 completed weeks of gestation (without use of maternal age)

SPR= Screen Positive Rates

Wald NJ, et alFirst and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Health Technology Assessment 2003; Vol. 7: No. 11

Advancement in Prenatal Trisomy Screening



Maternal Age

1960s

Detection rate 27%

Gestational age N/A

Chromosomes screened: All

MSAFP

1980s

Detection rate 36%

Gestational age 15wk+

Chromosomes screened: T21

Quadruple Screen

1996

Detection rate 70-81%

Gestational age 15wk+

Chromosomes screened: T21, T18

Triple Screen

1988

Detection rate 60-74%

Gestational age 15w+

Chromosomes screened: T21, T18

FTS NT/Serum

1997

Detection rate 80-95%

Gestational age 10-11wk

Chromosomes screened: T21, T18, T13

NIPT Quantitative MPSS

2011

Detection rate 66-99%

Gestational age 10w+

Chromosomes screened: T21, T18, T13, SCA

NIPT SNP Microarray

2012

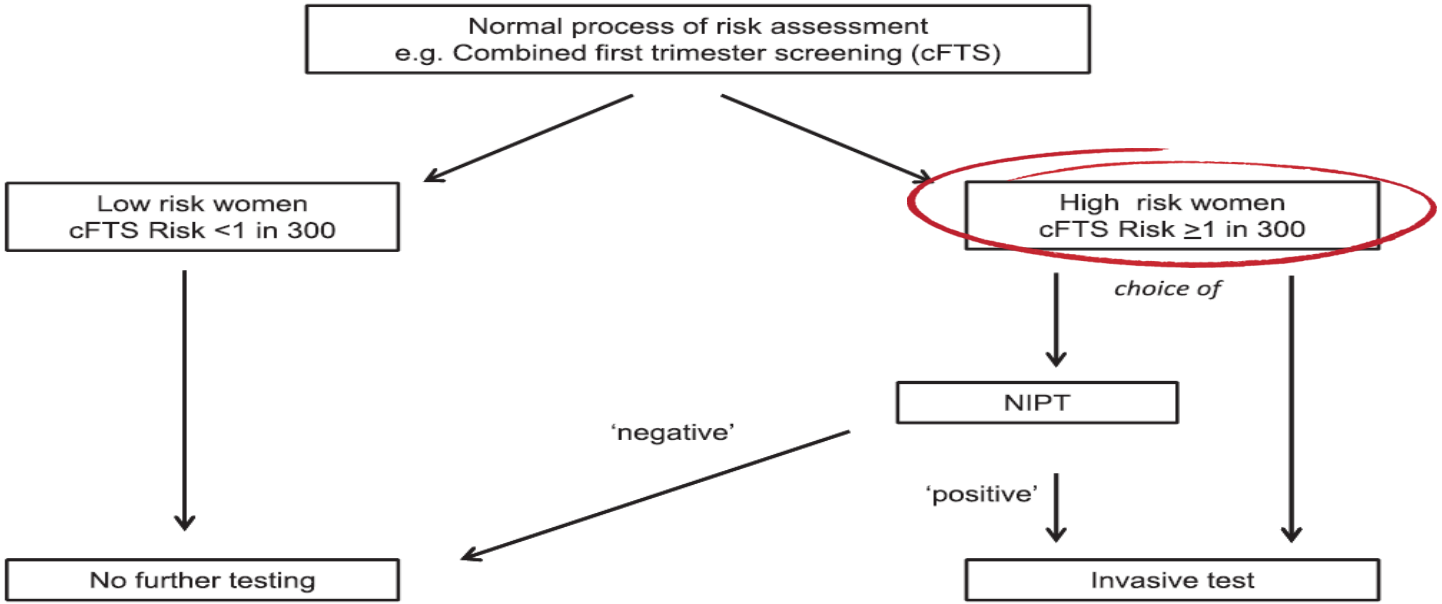
Detection rate 92-99%

Gestational age 9w+

Chromosomes screened: T21, T18, T13, SCA, Microdeletions

Contingency Model

cFTS & NIPT

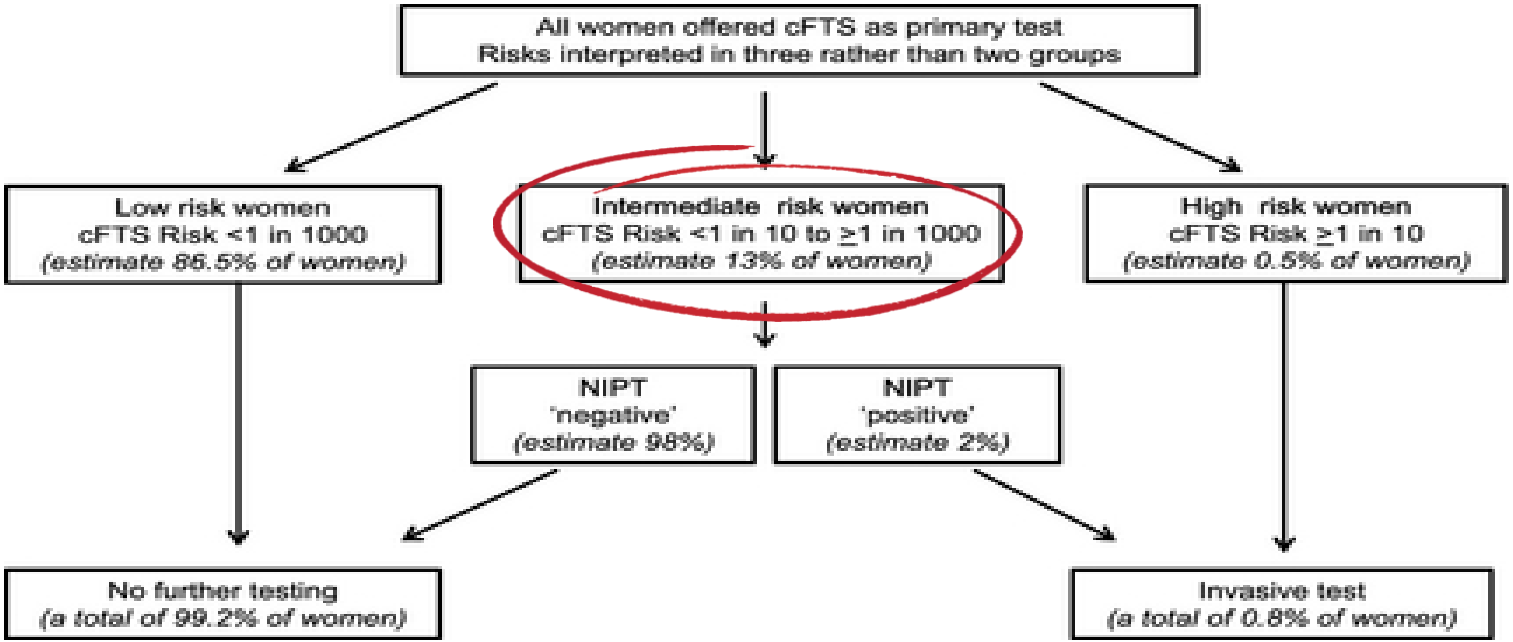


Women who are high risk are offered a choice of proceeding to NIPT or directly to invasive testing

Hui L and Hyett J. Australian and New Zealand Journal of Obstetrics and Gynaecology 2013; 53: 416–424

Contingency Model

cFTS & NIPT



Contingency model reduced the rates of invasive test

Hui L and Hyett J. Australian and New Zealand Journal of Obstetrics and Gynaecology 2013; 53: 416–424

Professional Society Guidelines

Summary of NIPT Information

Organization	Policy	Year
ACMG	Recommends “informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies”	2016
ACOG	“any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status”	2015
ASHG THE AMERICAN SOCIETY OF HUMAN GENETICS	“Different scenarios are possible, including NIPT as an alternative first tier option”	2015
ISPD	“ The following protocol options are currently considered appropriate: 1. cfDNA screening as a primary test offered to all pregnant women.”	2015

Professional Society Guidelines

Summary of Down Syndrome Screening Biomarkers

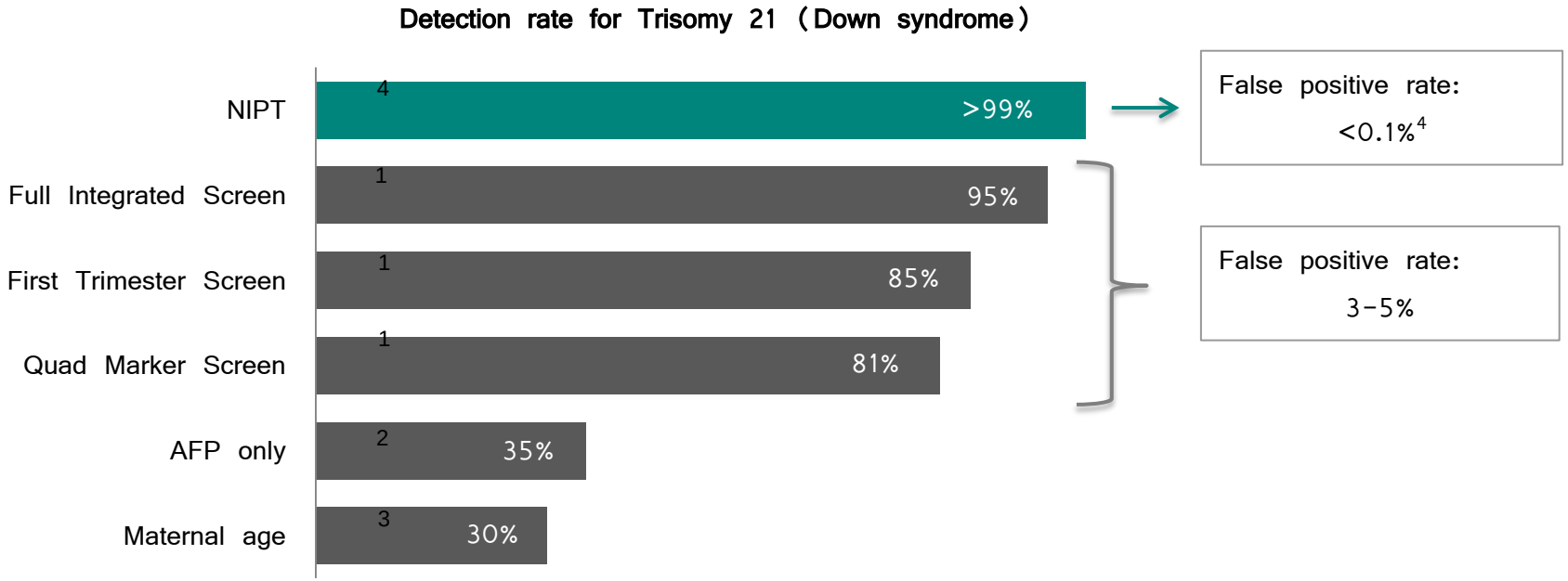
American College of Obstetricians and Gynecologists (ACOG)

- Use of both biochemical markers and nuchal translucency measurement is more effective than nuchal translucency measurement alone at detecting Down´s syndrome
- If first trimester screening is positive: offer genetic counseling and either chorionic villus sampling or second trimester amniocentesis
- Specific training, standardization for optimal NT measurement is important
- Even first trimester testing is done, it is still important to do second trimester screening for neural tube defects.

The Fetal Medicine Foundation

- The Fetal Medicine Foundation promotes screening for Down syndrome at $11-13^{+6}$ weeks by Nuchal Translucency (NT) or a combination of nuchal translucency and maternal serum biomarkers.
- The combination of nuchal translucency and maternal serum free ßhCG and PAPP-A improves the detection rate to 90%. There is evidence that the detection rate of 90% can be achieved with a reduction in the false positive rate from 5% to 2.5% by examining the nasal bone.

New possibilities in screening: Non-invasive prenatal testing



1. Ball et al. Obstet Gynecol. 2007 Jul;110(1):10-7. 2. Wald et al. BMJ. 1988 Oct 8;297(6653):883-7. 3. Thompson & Thompson Genetics in Medicine, Sixth Edition. Nussbaum, McInnes, Huntington. Saunders, 2001. 4. Norton M, et al, N Engl J Med. 2015 Apr 23;372(17):1589-97.

Limitations of conventional screening

1 in 20 women will receive a "positive" result[1]:

Vast majority will be "false positives"[2]

Referral to specialist, multiple office visits

Prolonged uncertainty, worry[3]

Risk of miscarriage with diagnostic testing options[4]

1. ACOG Practice Bulletin No. 77. Obstet Gynecol 2007;109:217-27. 2. Benn et al. Prenat Diagn. 2015 May 13. doi: 10.1002/pd.4608. [Epub ahead of print] 3. Acta Obstet Gynecol Scand. 2015 Jan;94(1):15-27. 4. Caughey et al. Obstet Gynecol 2006; 108(3 Pt 1): 612-6.

Limitations of conventional screening

19 in 20 women will receive a "negative" result:

But some of these women still have risk for trisomy

(due to 80-95% detection rate)

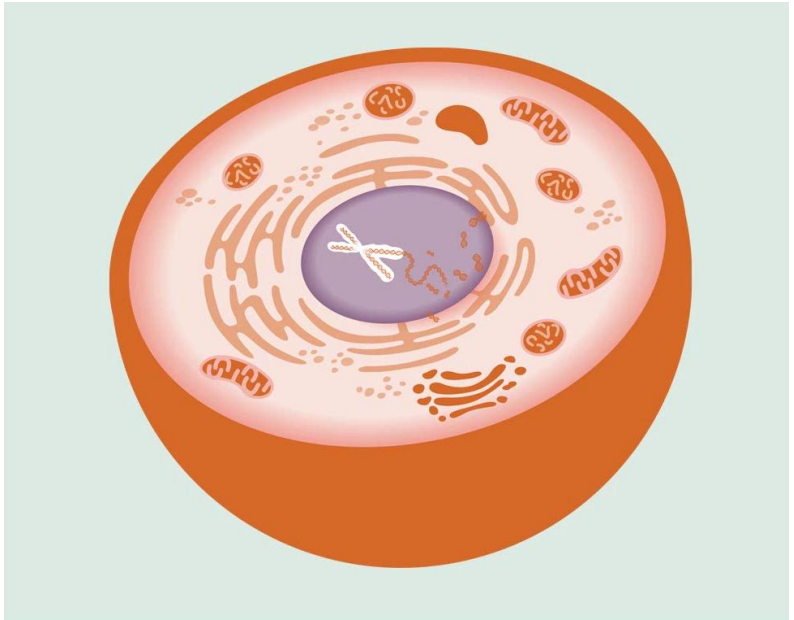
ACOG Practice Bulletin No. 77. Obstet Gynecol 2007;109:217-27.

Have we given the best for our baby?

Picture was taken from http://www.ashacarlos.com/blog/2012/04/10/pui-family-portrait-session/ accessed on 18-Oct-16

Prenatal cell-free DNA assessment

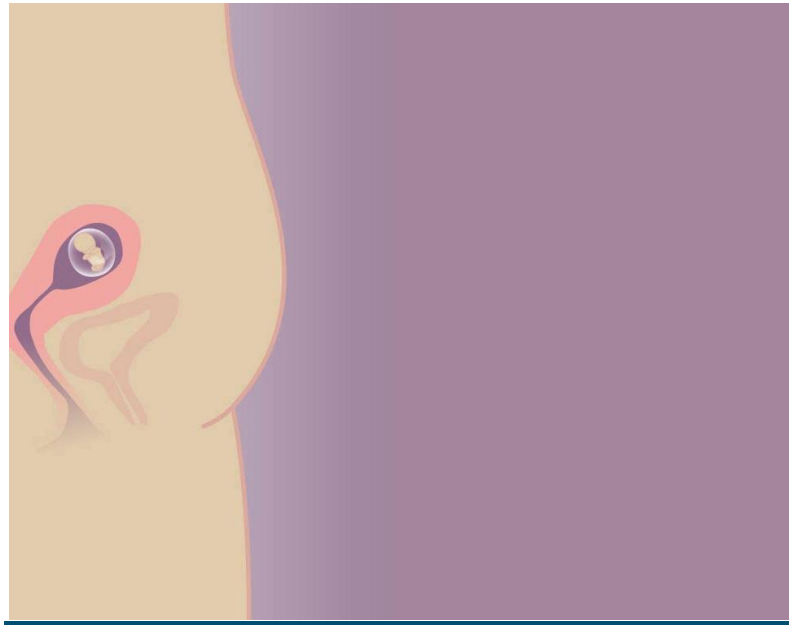
Standard Blood Draw



How it works

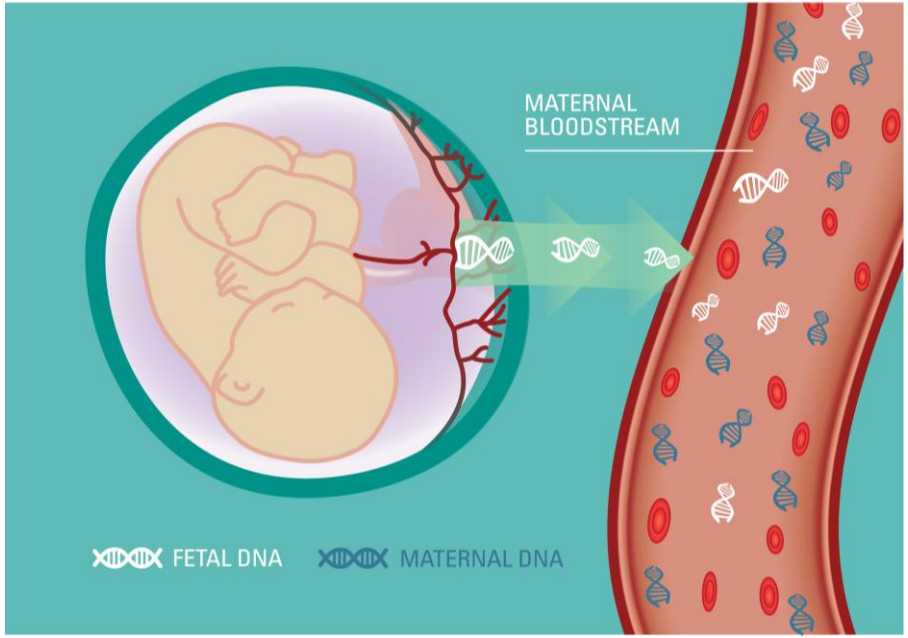
Prenatal cell-free DNA assessment

Standard Blood Draw



How it works

Non-invasive prenatal testing using cell-free DNA



- Cell-free DNA (cfDNA) are short DNA fragments
- During pregnancy, cfDNA from both the woman and fetus are present in maternal blood[1]
- Amount of fetal cfDNA present is a small fraction of the total cfDNA[2]
- Rapid clearance of fetal cfDNA after delivery (<24 hours)[3]

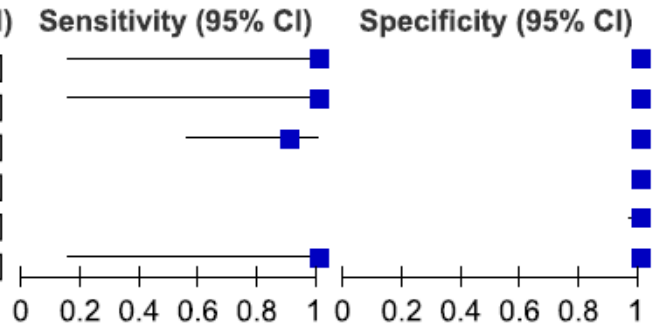
1. Lo et al. Lancet 1997;350:485-87. 2. Lo et al. Am J Hum Genet. 1998 Apr;62(4):768-75. 3. Lo et al. Am J Hum Genet 1999; 64:218-224.

Trisomy	Population Probability ("risk")	Sample size (no. of studies)	Sensitivity, pooled estimates (95% CI)	Specificity, pooled estimates (95% CI)	Quality of evidence	Rating items	True positive (TP) False positive (FP) False negative (FN) True negative (TN)
T21	High	107 474 (26)	0.998 (0.981–0.999)	0.999 (0.99–0.999)	(⊕⊕⊕O)	−1 Study design/quality	1839 TP 52 FP 8 FN 105 575 TN
T21	Average	62 201 (6)	0.993 (0.955–0.999)	0.999 (0.998–0.999)	(⊕⊕⊕O)	−1 Study design/quality	156 TP 37 FP 1 FN 62 107 TN
T18	High	146 465 (22)	0.977 (0.958–0.987)	0.999 (0.998–0.999)	(⊕⊕⊕O)	−1 Study design/quality	566 TP 70 FP 15 FN 146 129 TN
T13	High	137 078 (18)	0.975 (0.819–0.997)	0.999 (0.999–0.999)	(⊕⊕OO)	−1 Study design/quality −1 imprecision	134 TP 56 FP 10 FN 137 499 TN

TP, trisomy is verified; FP, incorrectly classified as trisomy; FN, trisomy is incorrectly classified as normal; TN, absence of trisomy is verified.
⊕⊕⊕O – moderate quality of evidence, ⊕⊕OO – limited quality of evidence.

(a)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bianchi 2014	2	3	0	1902	1.00 [0.16, 1.00]	1.00 [1.00, 1.00]
Nicolaides 2012	2	2	0	1945	1.00 [0.16, 1.00]	1.00 [1.00, 1.00]
Norton 2015	9	1	1	15830	0.90 [0.55, 1.00]	1.00 [1.00, 1.00]
Pergament 2014	0	0	0	474	Not estimable	1.00 [0.99, 1.00]
Shaw 2014	0	0	0	100	Not estimable	1.00 [0.96, 1.00]
Song 2013	2	1	0	1738	1.00 [0.16, 1.00]	1.00 [1.00, 1.00]



(b)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bianchi 2014	1	1	0	891	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]
Norton 2015	2	2	0	11181	1.00 [0.16, 1.00]	1.00 [1.00, 1.00]
Pergament 2014	2	0	0	472	1.00 [0.16, 1.00]	1.00 [0.99, 1.00]
Shaw 2014	0	0	0	100	Not estimable	1.00 [0.96, 1.00]
Song 2013	1	0	0	1740	1.00 [0.03, 1.00]	1.00 [1.00, 1.00]

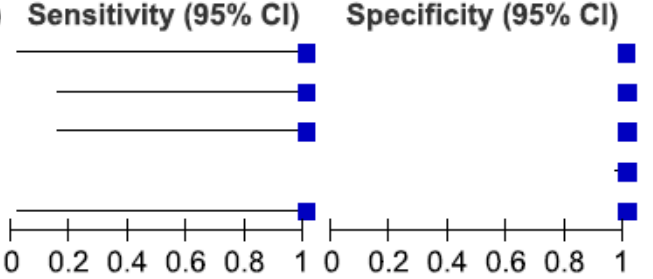


Figure 6. Meta-analysis of sensitivity and specificity of non-invasive prenatal testing (NIPT) in a population at average risk of carrying a fetus with chromosome aberration: (a) trisomy 18 (b) trisomy 13. [Color figure can be viewed at wileyonlinelibrary.com]

NEXT Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

Largest blinded prospective NIPT study to date

35 clinical sites in 6 countries（US, EU）

Norton M, et al, N Engl J Med. 2015 Apr 23;372(17):1589-97.

NEXT Study[1] – Objective & Background

Compare the performance of Harmony to traditional screening for trisomy 21 in a clinical setting

- Collect outcome data on all subjects

Powered for BOTH sensitivity and specificity

- Previous studies of NIPT in a general population were not large enough to evaluate sensitivity[2,3]

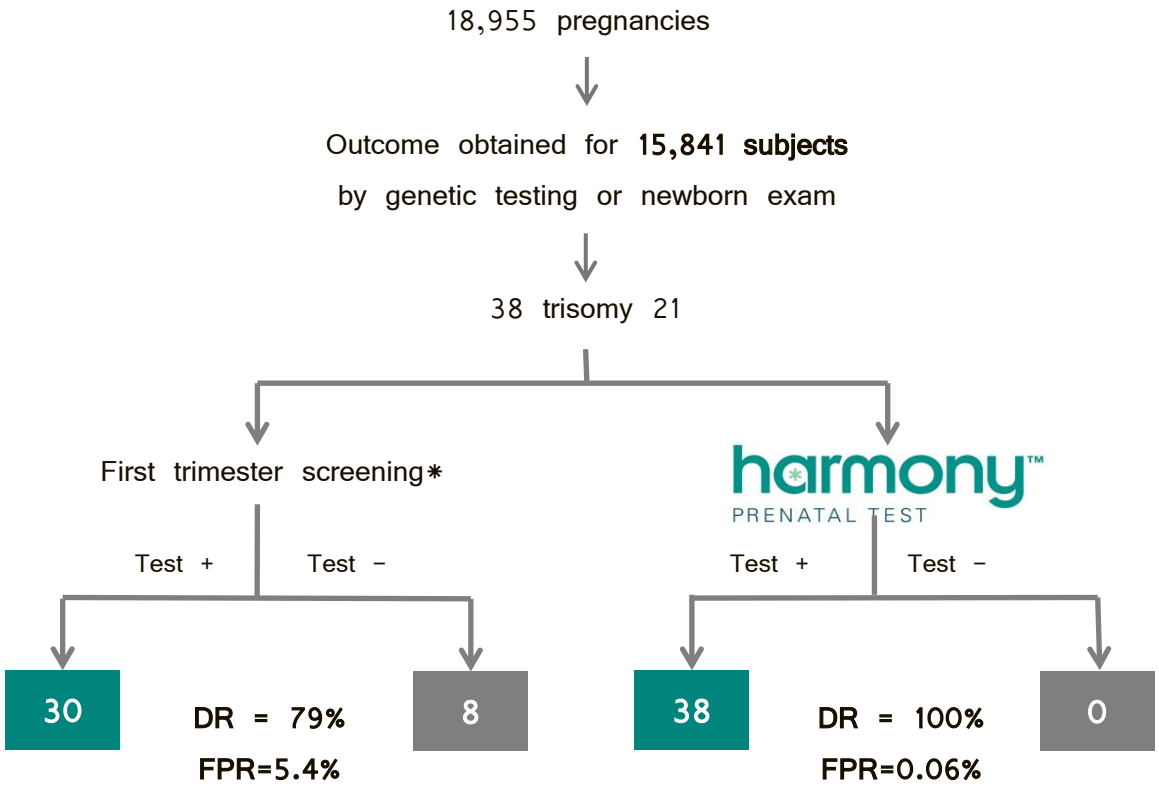
First trimester screening (FTS) and Harmony performed simultaneously for direct comparison

- Previous studies performed NIPT after the first trimester, when fetal fraction is higher[2,4]

1. Norton M, et al, N Engl J Med. 2015 Apr 23;372(17):1589-97. 2. Bianchi et al. N Engl J Med. 2014 Feb 27;370(9):799-808. 3. Nicolaides et al. Am J Obstet Gynecol. 2012 Nov;207(5):374.e1-6. 4. Wang et al. Prenat Diagn. 2013 Jul;33(7):662-6.

NEXT Study – Overview

Mean maternal age: 30.7 years
Mean gestational age: 12.5 weeks
Mean maternal weight: 65.8 kg



Norton M, et al, N Engl J Med. 2015 Apr 23;372(17):1589-97.
*hCG and PAPP-A, nuchal translucency measurement
DR = detection rate; FPR = false positive rate

Primary Analysis – Trisomy 21 Results

	FTS	Harmony	
Sensitivity	**79%** (30 of 38)	**100%** (38 of 38)	*p=0.008*
False Positive Rate	**5.4%** (854 of 15,803)	**0.06%** (9 of 15,803)	*p <0.001*
Positive Predictive Value	**3.4%**	**81%**	*p <0.001*

Overall Trisomy 21 Frequency = 38/15,841 (1 in 417)

Source: Norton M, et al, N Engl J Med. 2015 Apr 23;372(17):1589-97.

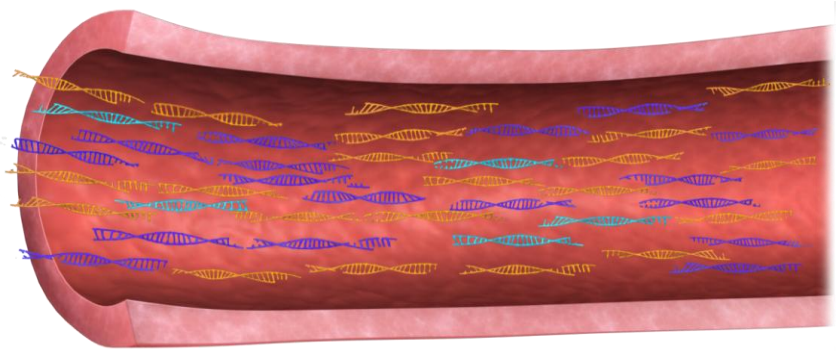
NEJM Harmony Study – Conclusions

Harmony is statistically superior to first-trimester screening for the detection of trisomy 21 in a general pregnancy population.

- Significantly Higher Detection Rate:
  - Harmony: 100%
  - FTS: 79%
- 90-fold Lower False-Positive Rate:
  - Harmony: 1 in 1,756
  - FTS: 1 in 19
- 20-fold Higher Positive Predictive Value:
  - Harmony: 81%
  - FTS: 3.4%

Source: Norton M, et al, N Engl J Med. 2015 Apr 23;372(17):1589-97.

Advantages of Directed Analysis （DANSR™）



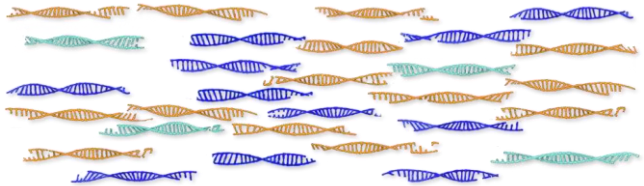
cfDNA in blood

Chr 21, 18, 13, X, Y cfDNA

Other Chr cfDNA

Unmapped cfDNA

Massively Parallel Shotgun Sequencing （MPSS）

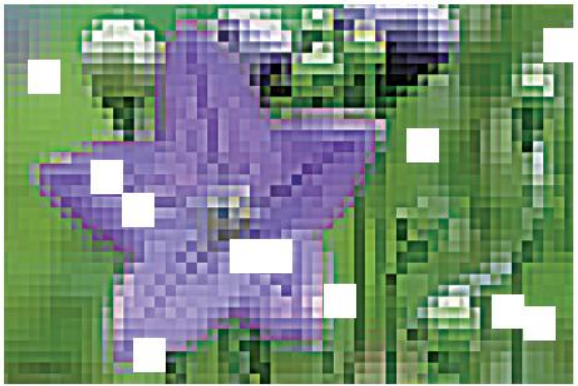


Directed analysis （DANSR）

The Harmony approach – Advantages of DANSR™

- Harmony provides the deepest analysis of chromosomes of interest
  - DANSR targets chromosomes of interest
  - Chromosomes 21, 18, and 13 represent <10% of the genome[1]

Original state of the genome

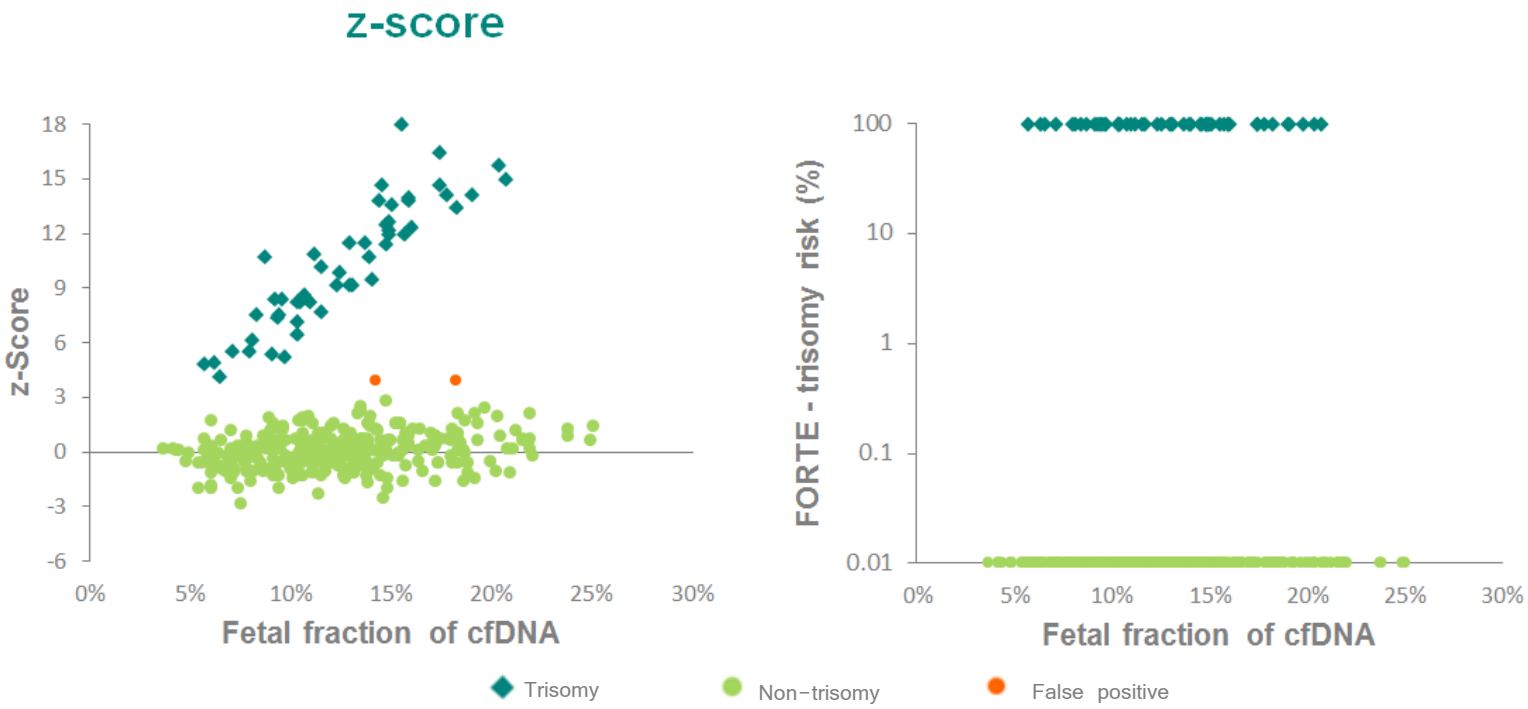


Random approach

Harmony approach

1. Lander et al. Nature 409, 860-921 (15 February 2001) doi:10.1038/35057062

DANSR result is analyzed with Fetal fraction Optimized Risk of Trisomy Evaluation （FORTE） algorithm



Ashoor G et al., Am J Obstet Gynecol. 2012 Apr;206(4):322.e1-5.

A combination of DANSR and FORTE for individualized probability score

Test Results — **Fetal cfDNA Percentage: 10.5%**

CHROMOSOME	RESULT	PROBABILITY	RECOMMENDATION
Trisomy 21 (T21)	**High Probability**	**Greater than 99/100 (99%)**	**Genetic counseling and additional testing**
Trisomy 18 (T18)	Low Probability	Less than 1/10,000 (0.01%)	Review results with patient
Trisomy 13 (T13)	Low Probability	Less than 1/10,000 (0.01%)	Review results with patient

Blood is drawn any time after 10 weeks gestation

DANSR™ Assay

Targeted analysis of chromosomes of interest

Accurately measures fetal fraction

FORTE™ Analysis

Incorporates:

- chromosome quantification
- fetal fraction
- maternal age
- gestational age

Harmony Report

Individualized probability score for each patient

Fetal fraction is reported

1. Sparks et al. Prenat Diagn. 2012 Jan;32(1):3-9. 2. Sparks et al. Am J Obstet Gynecol. 2012 Apr;206(4):319.e1-9.

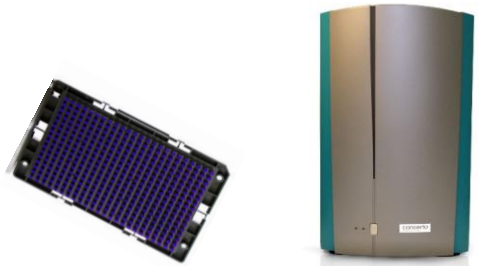
Evolution of cfDNA platform: from sequencing to microarray

Next Generation Sequencing (NGS)

HiSeq (Illumina)

"..Sample multiplexing is required to achieve economically efficient use of available sequence capacity.."

Microarray

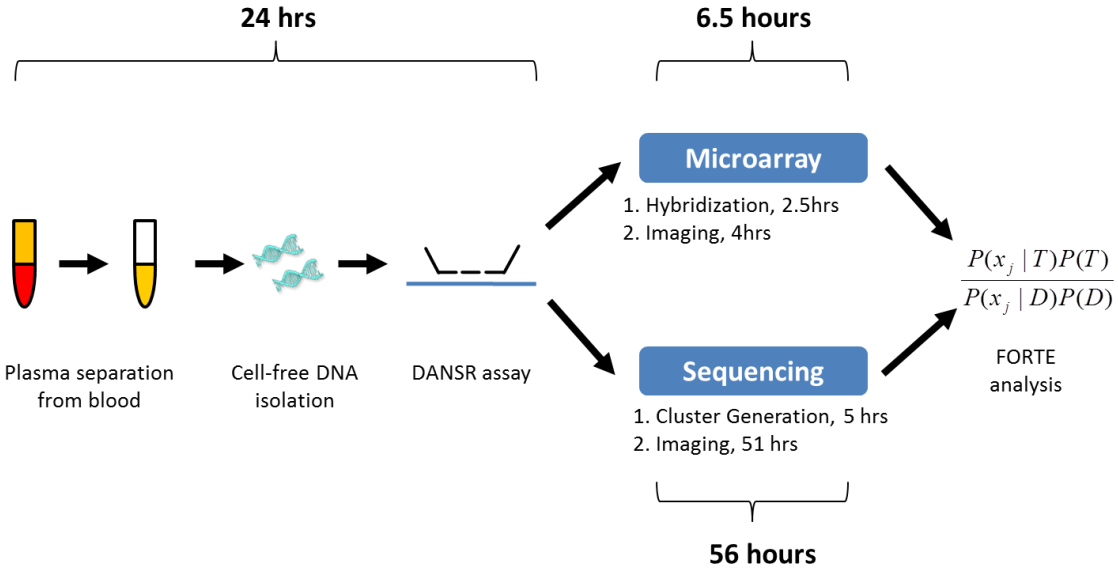


Ariosa Concerto™ Imager
Manufactured by Affymetrix

"..Each sample is hybridized individually to a single microarray.."

Source: Juneau K et.al. Fet Diag Th 2014 (online)

Increase efficiency in NIPT

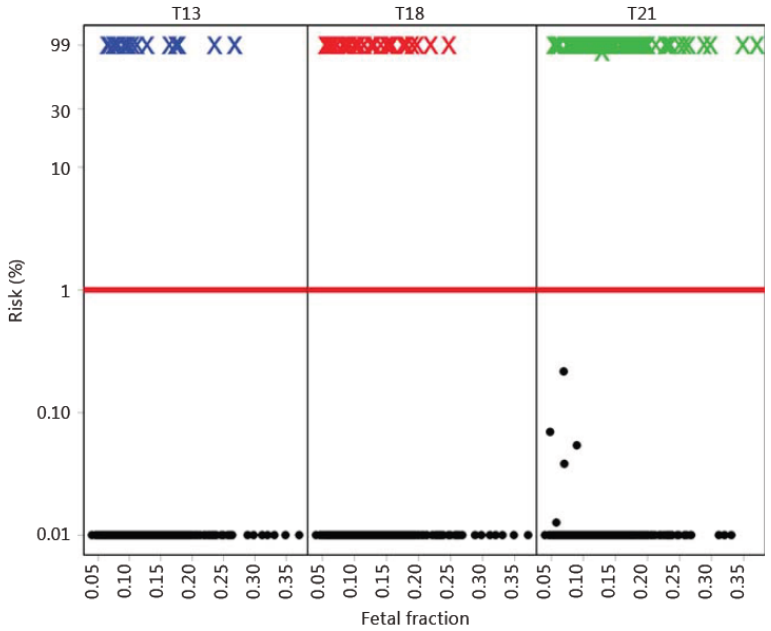


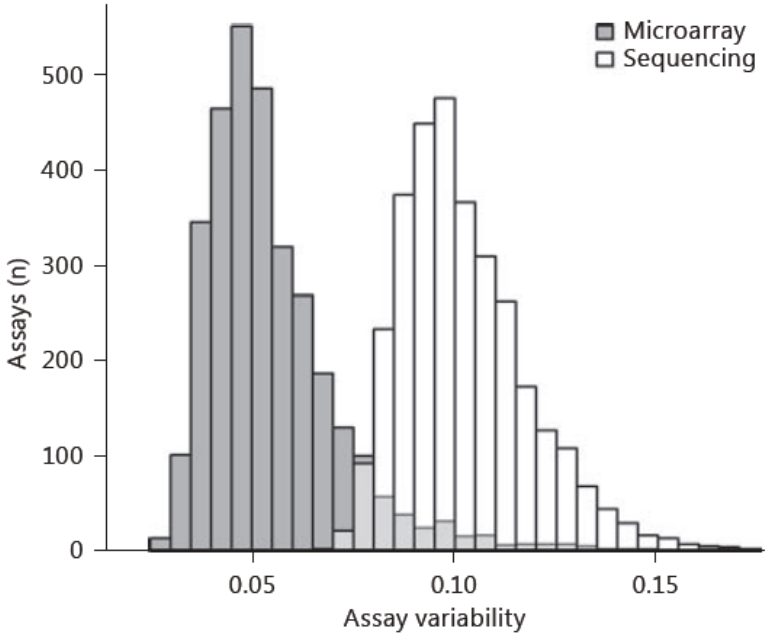
Number of samples per hour	
Microarray	64
Sequencing	12

"‥ Both microarray and sequencing technologies continue to improve. Some sequencing systems have accelerated sequencing modes that could decrease the time differential observed between microarrays and sequencing. However, in these modes, as the speed of sequencing increases, the capacity decreases and the cost per sample rises."

Juneau K et al. Fetal Diagn Ther. 2014;36(4):282-6.

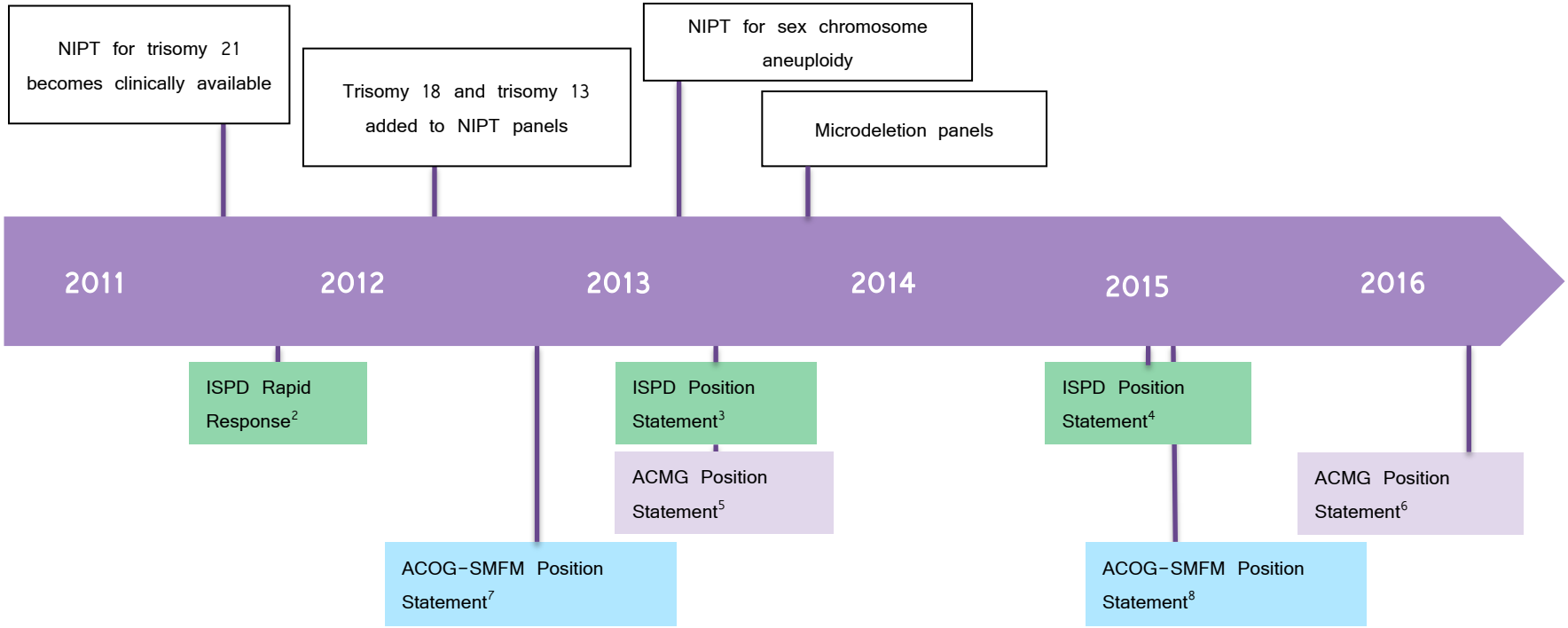
Less variability in assays and fetal fraction observed with microarray





Juneau K et al. Fetal Diagn Ther. 2014;36(4):282-6.

NIPT: Rapid Evolution

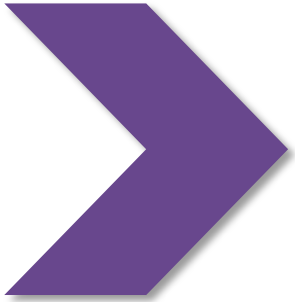


1. Allyse et al. Int J Womens Health. 2015;7:113-126. 2. Benn et al. Prenat Diagn. 2012 Jan;32(1):1-2. 3. Benn et al. Prenat Diagn. 2013 Jul;33(7):622-9. 4. Benn et al. Prenat Diagn. 2015 Aug;35(8):725-34. 5. Gregg et al. Genet Med. 2013 May;15(5):395-8. 6. Gregg et al. Genet Med. 2016 Jul 28. [Epub ahead of print] 7. Obstet Gynecol. 2012 Dec;120(6):1532-4. 8. Obstet Gynecol. 2015 Sep;126(3):e31-7.

Evolving clinical application of NIPT

"With suitable genetic counseling, MPS can be helpful for women who may have been determined to be **high risk** by one of the previously recommend screening strategies."

-International Society for Prenatal Diagnosis (ISPD), 2011[1]



"cfDNA screening as a primary test offered to **all** pregnant women [is considered appropriate]."

-International Society for Prenatal Diagnosis (ISPD), 2015[2]

1.Benn et al. Prenat Diagn. 2012 Jan;32(1):1-2. 2. Benn et al. Prenat Diagn. 2015 Aug;35(8):725-34.

Current professional guidelines: Low risk pregnancies

- International Society for Prenatal Diagnosis, 2015[1]:

  Appropriate to offer NIPT as a primary screening test to all pregnant women

- European and American Societies of Human Genetics, 2015[2]:

  NIPT as a first-tier screening test is an option

- American Congress of Obstetricians and Gynecologists/Society for Maternal Fetal Medicine, 2015[3]:

  NIPT should be offered to all women (but conventional methods are the appropriate choice for most women)

- American College of Medical Genetics and Genomics, 2016[4]:

  All pregnant women should be informed that NIPT is the most sensitive screening option for trisomy 21, trisomy 18, and trisomy 13

1. Benn et al. Prenat Diagn. 2015 Aug;35(8):725-34. 2. Dondorp et al. Eur J Hum Genet. 2015 Nov;23(11):1592. 3. ACOG Committee Position 640. Obstet Gynecol. 2015 Sep;126(3):e31-7. 4. Gregg et al. Genet Med. 2016 Jul 28. [Epub ahead of print]

DANSR and FORTE validation with microarray and NGS

DOI: 10.1002/pd.4686

PRENATAL **DIAGNOSIS**

ORIGINAL ARTICLE

Clinical performance of non-invasive prenatal testing (NIPT) using targeted cell-free DNA analysis in maternal plasma with microarrays or next generation sequencing (NGS) is consistent across multiple controlled clinical studies

Renee Stokowski[1], Eric Wang[1], Karen White[1], Annette Batey[1], Bo Jacobsson[2], Herb Brar[3], Madhumitha Balanarasimha[1], Desiree Hollemon[1], Andrew Sparks[1], Kypros Nicolaides[4] and Thomas J. Musci[1]*

Stokowski R et al. Prenat Diagn. 2015 Dec;35(12):1243-6.

DANSR and FORTE validation with microarray and NGS

Table 2 **Test Performance of DANSR/FORTE using microarray quantitation**

Diagnostic outcome	Subjects	Test high risk (chr)	Test low risk (chr)
Total subjects with results	791		
Euploid subjects	641	0/0/0 (21/18/13)	641/641/641 (21/18/13)
T21 subjects	108	107 (21)	1 (21)
T18 subjects	30	29 (18)	1[a] (18)
T13 subjects	12	12 (13)	0 (13)

Table 3 **Comprehensive clinical performance of DANSR/FORTE**

Characteristic	T21 test values	T18 test values	T13 test values
Total subjects	23 155	22 399	14 243
True positives	418	147	30
False positives	10	5	3
True negatives	22 724	22 243	14 208
False negatives	3	4	2
Sensitivity (95% CI)	99.3 (97.9–99.8)	97.4 (93.4–99.0)	93.8 (79.9–98.3)
Specificity (95% CI)	99.96 (99.92–99.98)	99.98 (99.95–99.99)	99.98 (99.94–99.99)

Stokowski R et al. Prenat Diagn. 2015 Dec;35(12):1243-6.

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Additional offerings

- **Twin pregnancies[1,2]**
  - Single result is reported for both fetuses
  - Fetal Sex assessment available for twin pregnancies
    - A male result indicates one or two male fetuses

    ∗Monosomy X and Sex Chromosome Aneuploidy Panel has not been validated in twin pregnancies

    ∗Harmony has not been validated in higher order multiples

- **NIPT validation for use in IVF pregnancies[3,4], including:**
  - Singleton or twin
  - Self or non-self egg donor
  - Surrogate pregnancies

1. Bevilacqua et al. Ultrasound Obstet Gynecol. 2015 Jan;45(1):61-6. 2. Gil et al. Fetal Diagn Ther. 2014;35:204-11. 3. Stokowski et al. Prenat Diagn. 2015;35:1-4. 4. Norton ME et al. N Engl J Med. 2015 Apr 1.

Performance in twin pregnancies

	Bevilacqua et al.[1] (prospective)	Gil et al.[2] (retrospective)	Gil et al.[2] (prospective)
Trisomy 21	11 of 12	9 of 10	2 of 2
Trisomy 18	5 of 5	–	1 of 1
Trisomy 13	–	1 of 1	–
Euploid	323 of 323	181 of 181	60 of 60

Identified as "High Risk":

- 22 of 24 cases of trisomy 21
- 6 of 6 cases of trisomy 18
- 1 of 1 case of trisomy 13
- No "false positives" in over 500 euploid cases

1. Bevilacqua et al. Ultrasound Obstet Gynecol. 2015 Jan;45(1):61-6. 2. Gil et al. Fetal Diagn Ther. 2014;35:204-11.

Incidence of sex chromosome aneuploidy （SCA）

Prevalence of common SCAs[1]:

- **47,XXY**（Klinefelter syndrome） 1/500–1/1,000 males
- **47,XXX**（Triple X syndrome） 1/1,000 females
- **47,XYY**（Jacobs syndrome） 1/1,000 males
- **45,X** （Turner syndrome） 1/2,500 females

Overall incidence of SCAs: ~1/500 live births

（Overall incidence of Down syndrome: ~ 1/800 live births[2]）

1. Thompson & Thompson Genetics in Medicine, Sixth Edition. Robert L. Nussbaum, Roderick McInnes, Willard Huntington. Saunders, 2001.
2. U.S. National Library of Medicine. Genetics Home Reference. Down Syndrome. http://ghr.nlm.nih.gov/condition/downsyndrome. Accessed Jan 25, 2016.

Performance for sex chromosome aneuploidies*

Karyotype	Identified as High Probability	%; 95%CI	False Positive	%; 95%CI
45,X	69/74	93; 85 - 97	2/496	0.4; 0.1-1.5
47,XXX	6/6	100; 61 - 100	3/496	0.6; 0.2-1.8
47,XXY	7/7	100; 65 - 100	0/496	0; 0.0-0.7
47,XYY	3/3	100; 44 - 100	0/496	0; 0.0-0.7

*CLIA laboratory experience

Nicolaides et al, Fetal Diagn Ther. 2014;35(1):1-6.

Hooks et al, Prenat Diagn. 2014 May;34(5):496-9.

Current professional guidelines: Microdeletions

- International Society for Prenatal Diagnosis, 2015[1]:

  Patients should be counseled regarding limitations. Testing should be limited to clinically significant disorders.

- European and American Societies of Human Genetics, 2015[2]:

  Currently not recommended

- American Congress of Obstetricians and Gynecologists/Society for Maternal Fetal Medicine, 2015[3]:

  Routine screening for microdeletions should not be performed

- American College of Medical Genetics and Genomics, 2016[4]:

  Patients should be informed of availability of testing, including limitations

1. Benn et al. Prenat Diagn. 2015 Aug;35(8):725-34. 2. Dondorp et al. Eur J Hum Genet. 2015 Nov;23(11):1592. 3. ACOG Committee Position 640. Obstet Gynecol. 2015 Sep;126(3):e31-7. 4. Gregg et al. Genet Med. 2016 Jul 28. [Epub ahead of print]

Conclusions

- All pregnant women should be screened for Down syndrome
- NIPT is targeted approach for specific chromosomes, i.e. T21, T13, T18
- Fetal fraction >4% is important for accurate result
- Microarray technology was developed to improve NGS platform with comparable performance and greater reproducibility
- DANSR and FORTE are validated to assess twin and IVF pregnancy
- Expanded menu will be made available in clinically relevant abnormalities, i.e. DiGeorge Syndrome

Thank You.