NIPT as Primary Screening for Down's Syndrome - Against

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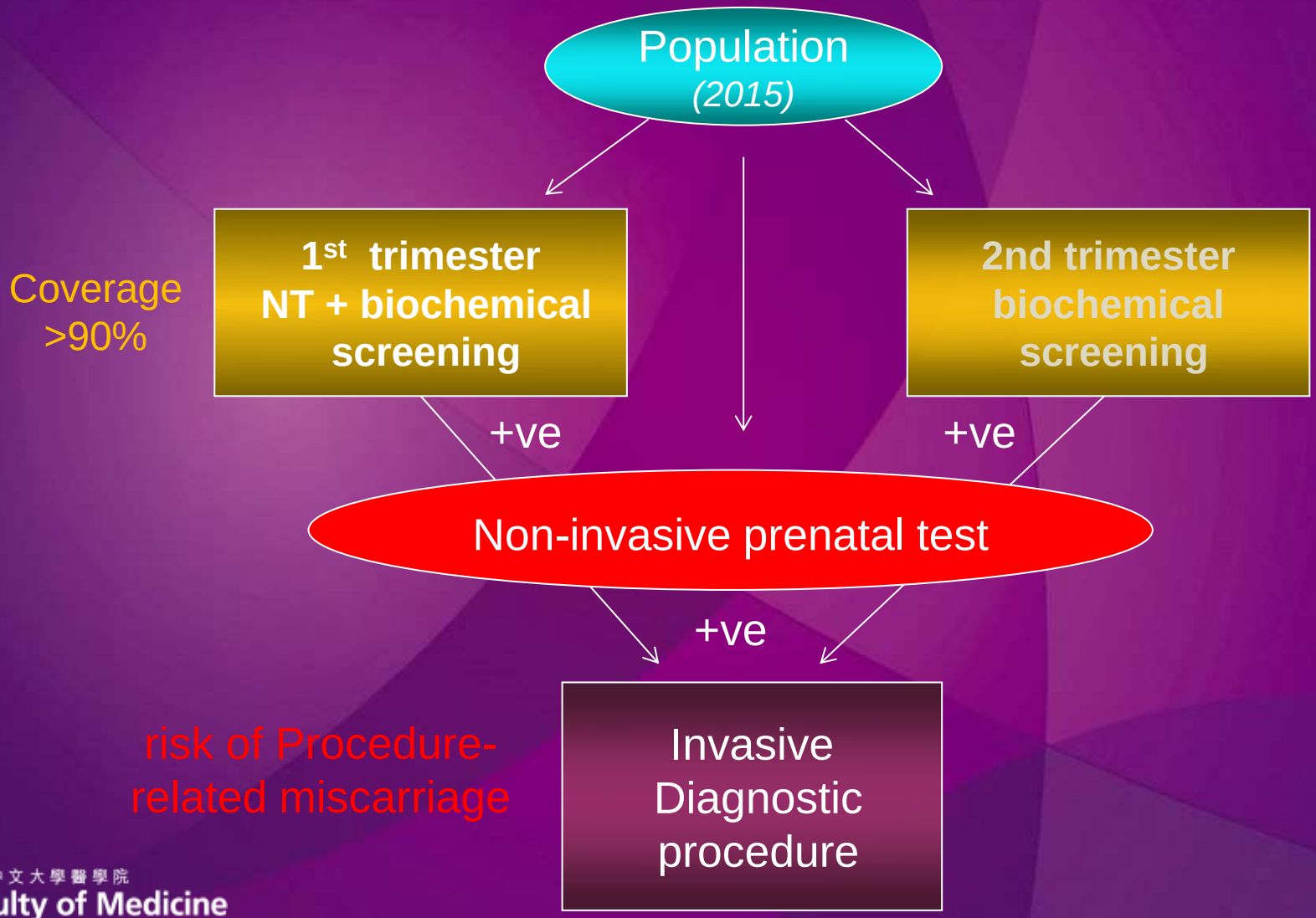
Current Universal Down's Screening Program In Hong Kong



First Trimester Down's Screening

Sensitivity: 90% False positive rate: 5%

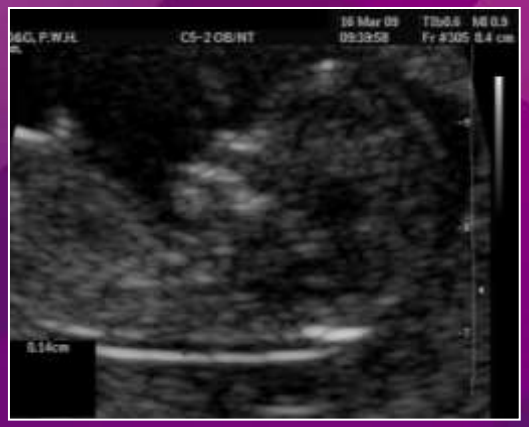
Risk = Background risk * LR_{NT}* LR_{HCG}* LR_{PAPPA}

Maternal history

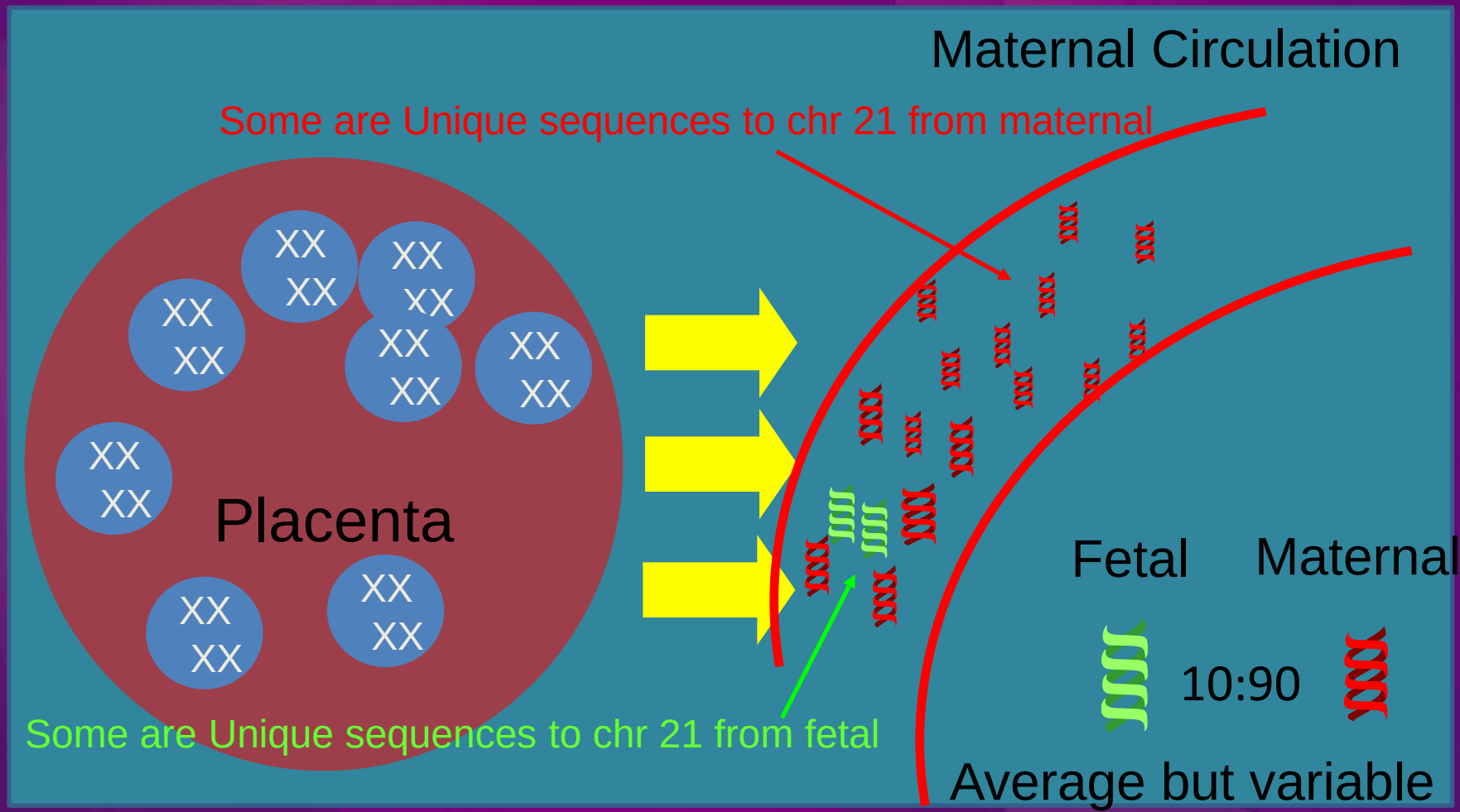
Nuchal Translucency

fbHCG

PAPP-A



Cell-free Fetal DNA in Maternal Plasma



Non-Invasive Prenatal Testing is 99 per cent accurate when screening for Down's syndrome

Test carries no risk of causing miscarriage unlike amniocentesis or CVS

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South China Morning Post

NIPT as Primary Screening for Down's Syndrome

⇓

NIPT to replace current universal combined screening

Comparison of cFTS vs NIPT

1. Detection rate
2. Missing abnormality
3. Procedure-related miscarriage
4. Cost-effectiveness
5. Potential problems

Comparison of cFTS vs NIPT

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NIPT as Primary Screening for Down's Syndrome

Performance

Based on 24 studies (1051 T21 and 21,608 euploidies)

	1st tri combined	Invasive test	NIPT T21
Sensitivity	90%	100%	99.2%
False + rate	5%	0%	0.09%

1. **Detecting more babies with Down's**
2. **Less invasive procedure → less miscarriage**

NIPT is very accurate but still a screening

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NIPT as Primary Screening for Down's Syndrome

Performance

Based on 24 studies (1051 T21 and 21,608 euploidies)

	1st tri Combined T21	1st tri Combined T13/18	NIPT T21	NIPT T18	NIPT T13	NIPT FPR
Sensitivity	90%	95%	99.2%	96.3%	91%	
False + rate	----- 5% ----		0.09%	0.13%	0.13%	0.35%

NIPT is very accurate but still a screening

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How about other chromosomal abnormality

- T18 DR 96.3%; FPR 0.13%
- T13 DR 91%; FPR 0.13%

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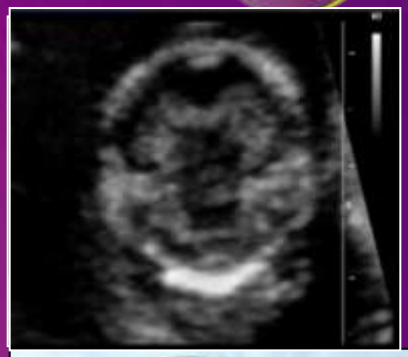
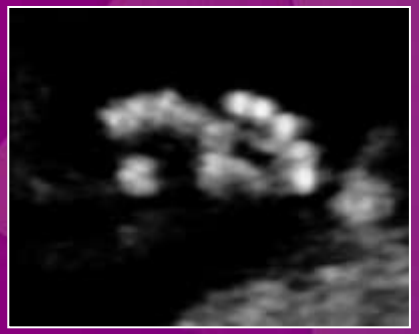
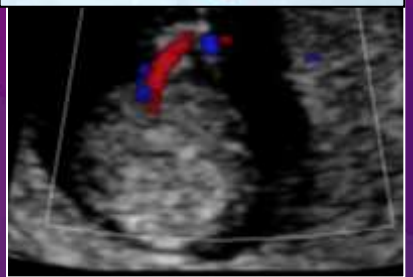
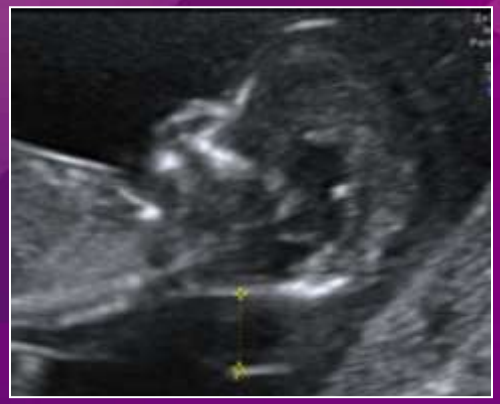
- Sex chromosome
- Chromosome rearrangement
- Huge NT
- Use of prenatal microarray (Additional 5-10% Pathogenic CNV's)









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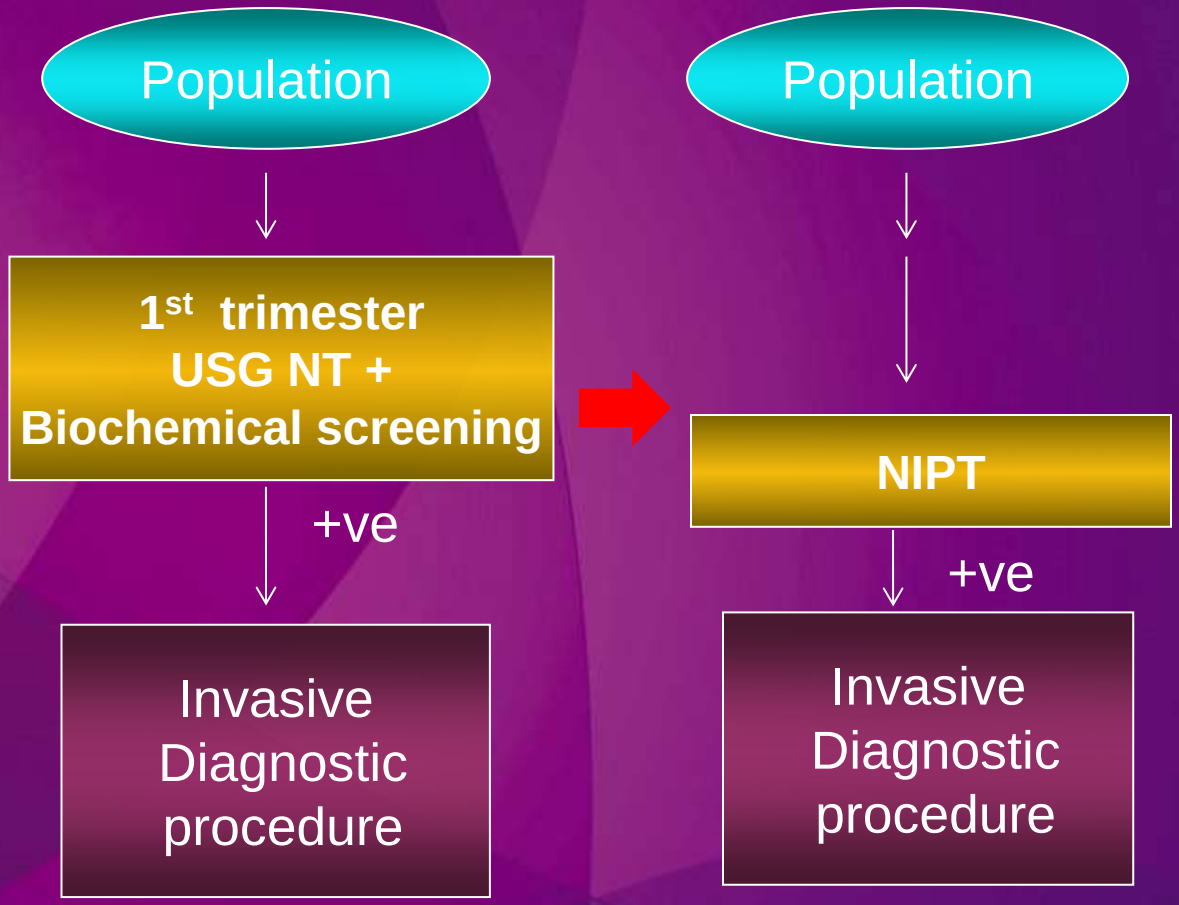
Convert the combined DSS to NIPT

- ACMG :
- ~50% of cytogenetic abnormalities detected by amniocentesis will not be detected if only trisomy 13,18,21 are the only aneuploidies being screened

- Susman et al:
- combined DSS vs universal NIPT →17% atypical chromosomal abnormality wound be missed



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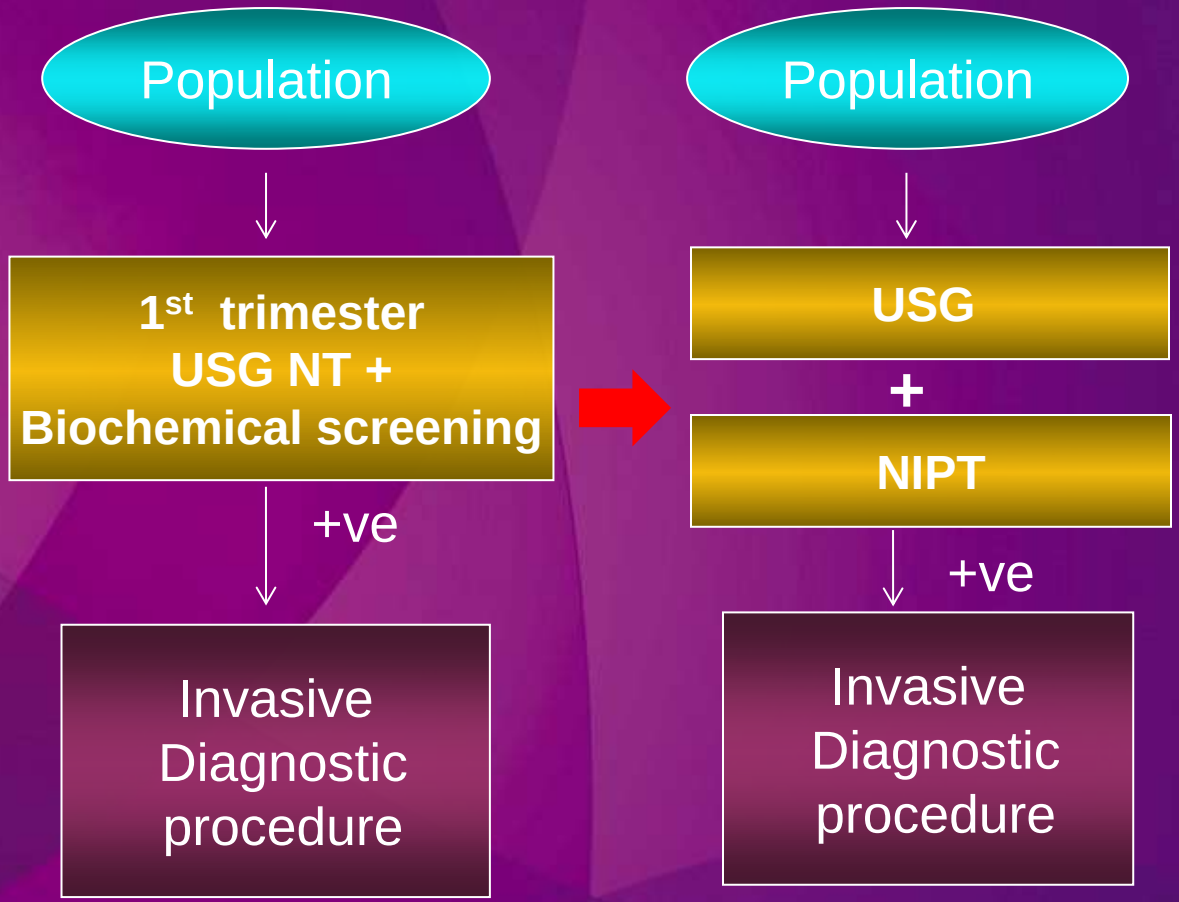

Professional Society Groups

Local Downs screen +ve pregnancies since July 2010-2014

T21 DR91% 83

Chromosomal Abnormality		Fetuses	NT>=3mm
Trisomy 21	Detectable by cffDNA	83	45%
Trisomy 18		37	38%
Trisomy 13		21	62%
Turners		15	93%
Chromosome Mosaic	High NT 26 (55%)	8	38%
Chromosomal Translocation		6	67%
Chromosome Rings		2	0%
Deletion		2	50%
47 XXX		3	0%
47 XXY		2	50%
Triploidy		1	0%
Other		8	38%

Incidental aneuploidy detected in 25% (including sex chr)
14% (excluding sex chr)

Comparison of cFTS vs NIPT

1. Detection rate
2. Missing abnormality
3. Procedure-related miscarriage
4. Cost-effectiveness
5. Potential problems

What is aim of providing screening ?

Comparison of cFTS vs NIPT

1. Detection rate
2. Missing abnormality
3. Procedure-related miscarriage
4. Cost-effectiveness
5. Potential problems

NIPT – False positive rate

Based on 24 studies (1051 T21 and 21,608 euploidies)

	1st tri Combined T21	1st tri Combined T13/18	NIPT T21	NIPT T18	NIPT T13	NIPT Sex chr	NIPT FPR
Sensitivity	90%	95%	99.2%	96.3%	91%		
False + rate	----- 5% ----		0.09%	0.13%	0.13%	0.37%	0.72%

NIPT is very accurate but still a screening

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NIPT
No results

Study	Method	GA (weeks)	Aneuploidy	Inadequate sample (n (%))	Laboratory failure (n (%)) Total	Low FF (< 4%)	Assay failure
Laboratory failure not reported							
Singleton pregnancy							
Shaw (2013)[73]	MPSS	> 12	T21, T18, T13, SCA				
Twin pregnancy							
Canick (2012)[47]	MPSS	14 (10–18)	T21, T13				
No data on low FF as reason for laboratory failure							
Singleton pregnancy							
Chen (2011)[2]	MPSS	—	T18, T13		0/289 (0.0)		
Chiu (2011)[41]	MPSS	13 (—)	T21	46/810 (5.7)	11/764 (1.4)		
Schnert (2011)[44]	MPSS	15 (10–28)	T21, T18		1/47 (2.1)		
			SCA		1/47 (2.1)		
Ashoor (2012)[45]	CSS	12 (11–13)	T21, T18	25/425 (5.9)	3/400 (0.8)		
Jiang (2012)[48]	MPSS	— (10–34)	T21, T18, T13		0/903 (0.0)		
			SCA		1/903 (0.1)		
Lau (2012)[49]	MPSS	12 (11–28)	T21, T18, T13, SCA		0/108 (0.0)		
Palomaki (2012)[52]	MPSS	14 (9–22)	T21, T18, T13		17/1988 (0.9)		
Sparks (2012)[53]	CSS	18 (11–36)	T21, T18		8/338 (2.4)		
Ashoor (2013)[54]	CSS	12 (11–13)	T13		62/2167 (2.9)		
Lau (2013)[56]	MPSS	13 (11–20)	T21		0/12 (0.0)		
Grömminger (2014)[66]	MPSS	15 (10–18)	T21		0/56 (0.0)		
Huang (2014)[69]	MPSS	19 (11–36)	T21, T18		0/189 (0.0)		
Details given on reason for laboratory failure							
Singleton pregnancy							
Ehrich (2011)[42]	MPSS	16 (8–36)	T21	13/480 (2.7)	18/467 (3.9)	7/467 (1.5)	11/467 (2.4)
Palomaki (2011)[43]	MPSS	15 (8–21)	T21		13/1696 (0.8)	9/1696 (0.5)	4/1696 (0.2)
Bianchi (2012)[46]	MPSS	15 (10–23)	T21, T18, T13	2/534 (0.4)	30/532 (5.6)	16/532 (3.0)	14/532 (2.6)
			SCA		65/532 (12.2)	16/532 (3.0)	49/532 (9.2)
Nicolaides (2012)[50]	CSS	12 (11–13)	T21, T18	100/2149 (4.7)	100/2049 (4.9)	46/2049 (2.2)	54/2049 (2.6)
Norton (2012)[51]	CSS	16 (10–38)	T21, T18	104/4002 (2.6)	148/3228 (4.6)	57/3228 (1.8)	91/3228 (2.8)
Verweij (2013)[62]	CSS	14 (10–28)	T21	30/595 (5.0)	16/520 (3.1)	7/520 (1.3)	9/520 (1.7)
Hall (2014)[67]	SNP	16 (12–22)	T13		4/68 (5.9)	4/68 (5.9)	
Nicolaides (2014)[70]	CSS	12 (11–13)	SCA		5/177 (2.8)	4/177 (2.3)	1/177 (0.6)
Pergament (2014)[71]	SNP	14 (7–40)	T21, T18, T13, SCA		85/1051 (8.1)	64/1051 (6.1)	21/1051 (2.0)
Quezada (2015)[75]	CSS	10 (10–11)	T21, T18, T13	1/2905 (0.03)	53/2905 (1.8)	38/2905 (1.3)	15/2905 (0.52)
Twin pregnancy							
del Mar Gil (2014)[65]	CSS	13 (12–13)	T21, T18, T13		15/207 (7.2)	11/207 (5.3)	4/207 (1.9)

No results rate ranged from 0 - 12.2%

Exclude inadequate sample and transport problem → still 0-6.3%

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Failure Rate

Table 3 Failure rates in 11 studies of cell-free DNA testing*

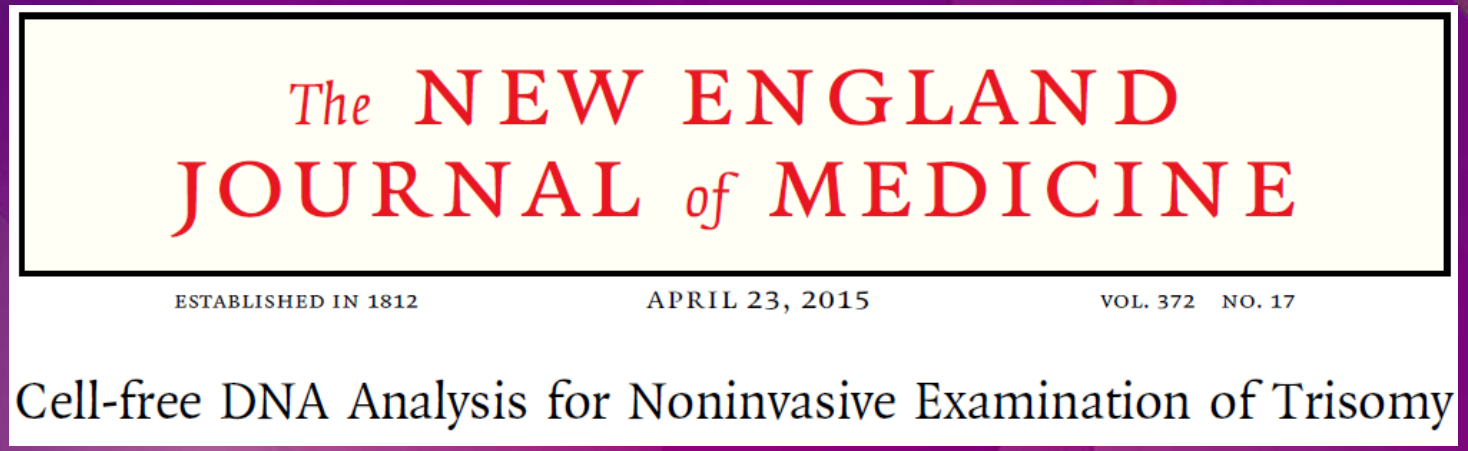
Trial	*Failure rate* (n *(%))*	*Reasons for failure*
Chiu *et al.*[65]	11/764 (1.4)	Low total DNA ($n=2$), low DNA library concentration ($n=8$), low matched DNA sequence reads ($n=1$)
Ehrich *et al.*[66]	18/467 (3.8)	Low % fetal DNA (< 4%) ($n=7$), low total DNA (< 556 copies) ($n=7$), low DNA library concentration (< 32.3 nM) ($n=15$), low number unique DNA sequence counts (< 3 million) ($n=11$); some failed more than one criteria
Palomaki *et al.*[67]	13/1696 (0.8)	Low % fetal DNA (< 4%) ($n=6$), other QC parameters ($n=7$): low DNA library concentration (< 25 nM) and low matched DNA sequence reads (< 12.5 million)
Bianchi *et al.*[68]	16/532 (3.0)	No fetal DNA
Sparks *et al.*[70]	8/338 (2.4)	Low % fetal DNA (< 3%), low DNA sequence counts, evidence from SNPs of non-singleton pregnancy
Ashoor *et al.*[69]	3/400 (0.8)	Amplification and sequencing
Norton *et al.*[71]	148/3228 (4.6)	Low % fetal DNA (< 4%) ($n=57$), assay failure ($n=91$): inability to measure % fetal, high variation in DNA counts and failed sequencing
Lau *et al.*[73]	0/567 (0.0)	—
Nicolaides *et al.*[74]	100/2049 (4.9)	Low % fetal DNA (< 4%) ($n=46$), assay failure ($n=54$)
Dan *et al.*[39]	79/11 184 (0.7)	Quality of separation, extraction, sample preparation and sequencing: low peak DNA library size, low library concentration (< 30 nM) and low matched DNA sequence reads (< 2 million)
Gil *et al.*[78]	40/997 (4.0)	Low % fetal DNA (< 4%) ($n=23$), assay failure ($n=17$)

*Excluding tests rejected because of inadequate sample quality.

Redraw and retest → still ½ cases failure

Benn et al UOG 2013

No results ? Invasive test



- Porspective multicenters (35)
- 15,841 participants
- 3% no results rate
- Among no results group, 2.7% aneuploidy vs 0.4% in overall cohort
- Estimation :
  - 40,000 x 3% x 2.7% = 33

NIPT – False positive rate

Based on 24 studies (1051 T21 and 21,608 euploidies)

	1st tri Combined T21	1st tri Combined T13/18	NIPT T21	NIPT T18	NIPT T13	NIPT Sex chr	NIPT FPR
Sensitivity	90%	95%	99.2%	96.3%	91%		
False + rate	----- 5% ----		0.09%	0.13%	0.13%	0.37%	0.72% +

No results: 3.2%

→ 4%

Gil et al UOG 2015

ORIGINAL ARTICLE

Prospective assessment of the Hong Kong Hospital Authority universal Down syndrome screening programme

Daljit S Sahota 邵浩達
WC Leung 梁永昌
WP Chan 陳運鵬
William WK To 杜榮基
Elizabeth T Lau 劉嚴德光
TY Leung 梁德楊

Objective To evaluate the performance of the locally developed universal Down syndrome screening programme.

Design Population-based cohort study in the period July 2010 to June 2011 inclusive.

Setting Four Hong Kong Hospital Authority Departments of Obstetrics and Gynaecology and a central university-based laboratory for maternal serum processing and risk determination.

Participants Women were offered either a first-trimester combined test (nuchal translucency, free beta human chorionic gonadotropin, and pregnancy-associated plasma protein-A) or nuchal-translucency-only test, or a second-trimester double test (alpha-fetoprotein and total human chorionic gonadotropin) for detection of Down syndrome according to their gestational age. Those with a trisomy 21 term risk of 1:250 or higher were offered a diagnostic test.

Results A total of 16 205 pregnancies were screened of which 13 331 (82.3%) had a first-trimester combined test, 125 (0.8%) had a nuchal-translucency test only, and 2749 (17.0%) had a second-trimester double test. There were 38 pregnancies affected by Down syndrome. The first-trimester screening tests had a 91.2% (31/34) detection rate with a screen-positive rate of 5.1% (690/13 456). The second-trimester test had a 100% (4/4) detection rate with a screen-positive rate of 6.3% (172/2749). There were seven (0.9%) pregnancies that miscarried following an invasive diagnostic test. There were two Down syndrome–affected live births, both with an estimated first-trimester trisomy 21 term risk lower than 1:250.

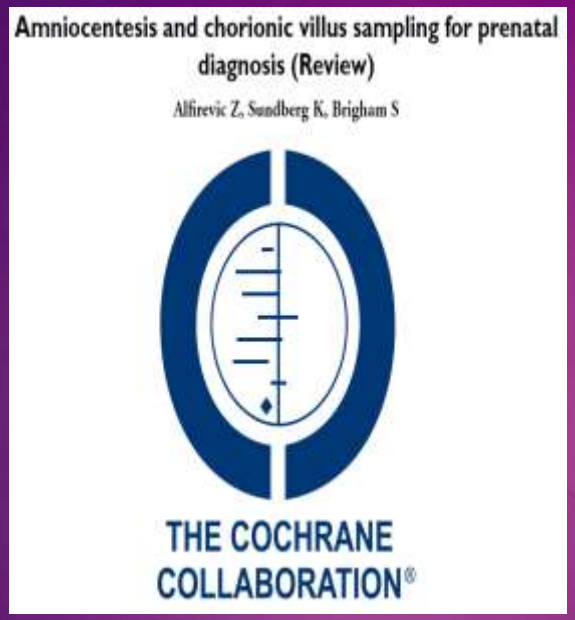
MISCARRIAGE RATE ≈ 0.9%
(NOT EXLCUDING BACKGROUND RATE)

Key words
Down syndrome; First trimester screening; Second trimester screening; Nuchal translucency; Quality control

Hong Kong Med J 2013;19:101-8

Cost-effectiveness of NIPT in Practice

Iatrogenic Loss / Procedure Loss Rates



Procedure Loss Rate after amnio ≈ 1%

Study by A Tabor et al 1986

Background miscarriage rate

Improvement in amnio/CVS performance over last 30 yrs?

Update on Procedure-Related Risks for Prenatal Diagnosis Techniques

Ann Tabor[a] Zarko Alfirevic[b]

Procedure Loss Rate ≈ 0.5-1%

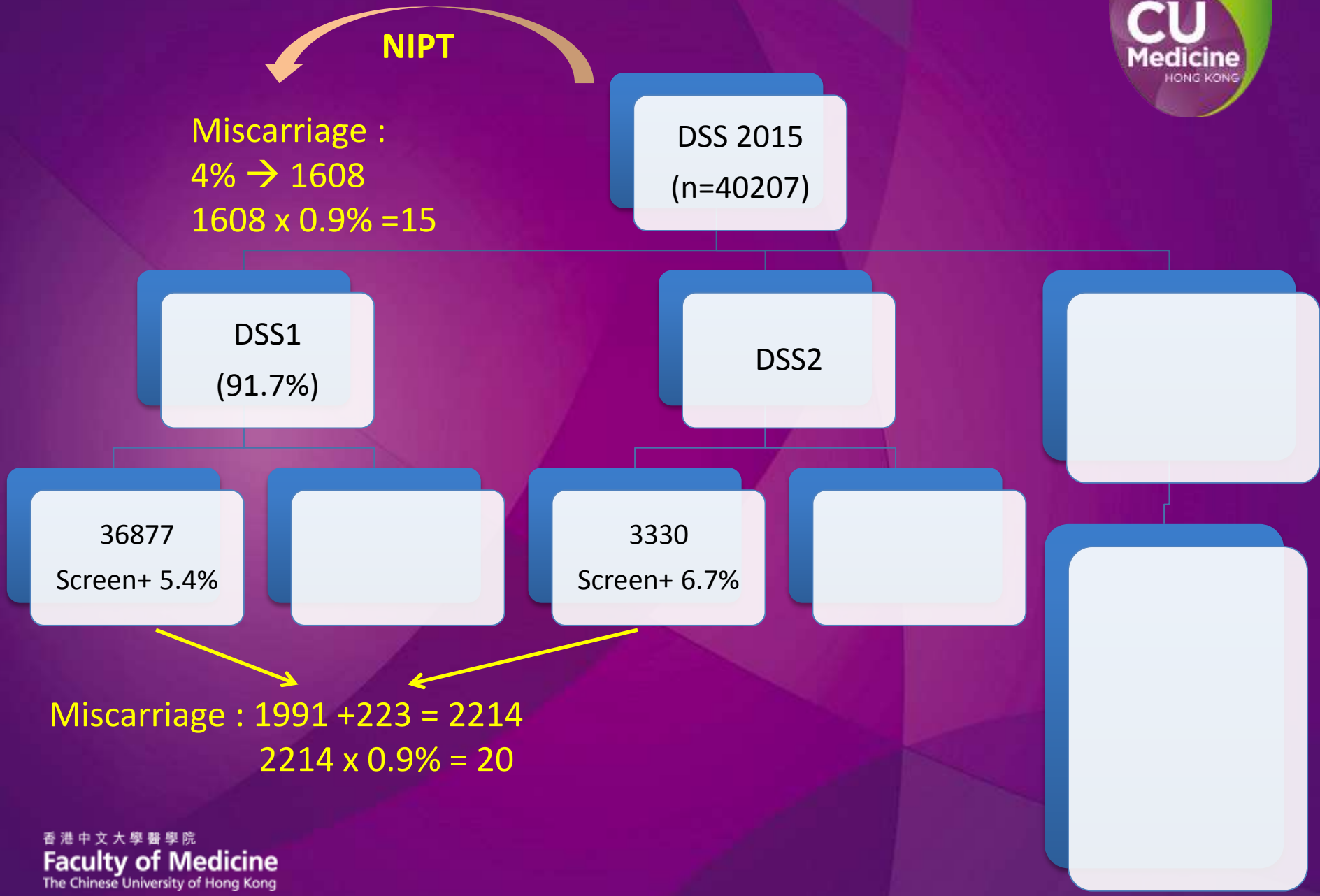
Fetal Diagn Ther 2010

Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis

Procedure Loss Rate Amnio ≈ 0.11%
CVS ≈ 0.22%

Ranjit Akolekar[1,2], Jaroslaw Beta[1], Gemma Picciarelli[1], Caroline Ogilvie[3], Francesco D'Antonio[4]

UOG 2014



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Comparison of cFTS vs NIPT

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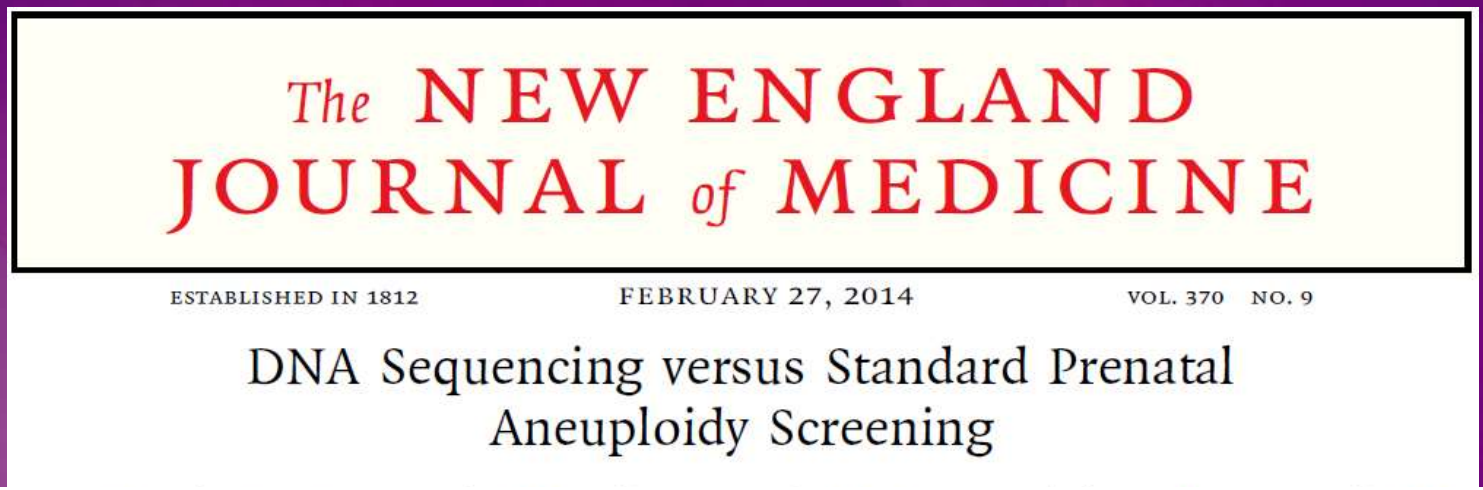
cffDNA General Population

cffDNA Performance in low risk and high risk should be similar



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 27, 2014 VOL. 370 NO. 9

DNA Sequencing versus Standard Prenatal Aneuploidy Screening

"One of the issues with respect to whether a certain test should be recommended inevitably has to include the issue of cost. Until everybody has a good understanding of what this test is going to cost globally for large numbers of patients, I think we have to be careful about what we recommend ..... replacing the current technology"

Associate Editor, The New England Journal of Medicine

Costs for large populations ?

Recent cost studies for implementing cffDNA Test

Clinical utility and cost of non-invasive prenatal testing with cfDNA analysis in high-risk women based on a US population

Ken Song[1], Thomas J. Musci[1], and Aaron B. Caughey[2]

[1]*Ariosa Diagnostics, Inc., San Jose, CA, USA and* [2]*Oregon Health & Science University, Portland, OR, USA*

J Matern Fetal Neonatal Med, 2013; 26(12): 1180–1185

?

Harmony Test

Targeted analysis

2013

OPEN ACCESS Freely available online

PLOS | ONE

Model-Based Analysis of Costs and Outcomes of Non-Invasive Prenatal Testing for Down's Syndrome Using Cell Free Fetal DNA in the UK National Health Service

Stephen Morris[1]*, Saffron Ka... Melissa Hill[3,4], Lyn S. Chitty[3,4]

1 Department of Applied Health Research, Univers... Kingdom, 2 NHS Fetal Anomaly Screening Programme, University of Exeter, Exeter, United Kingdom, 3 Clinical and Molecular Genetics ... Health and Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, 4 Fetal Medicine Unit, University Co... HS Foundation Trust, London, United Kingdom

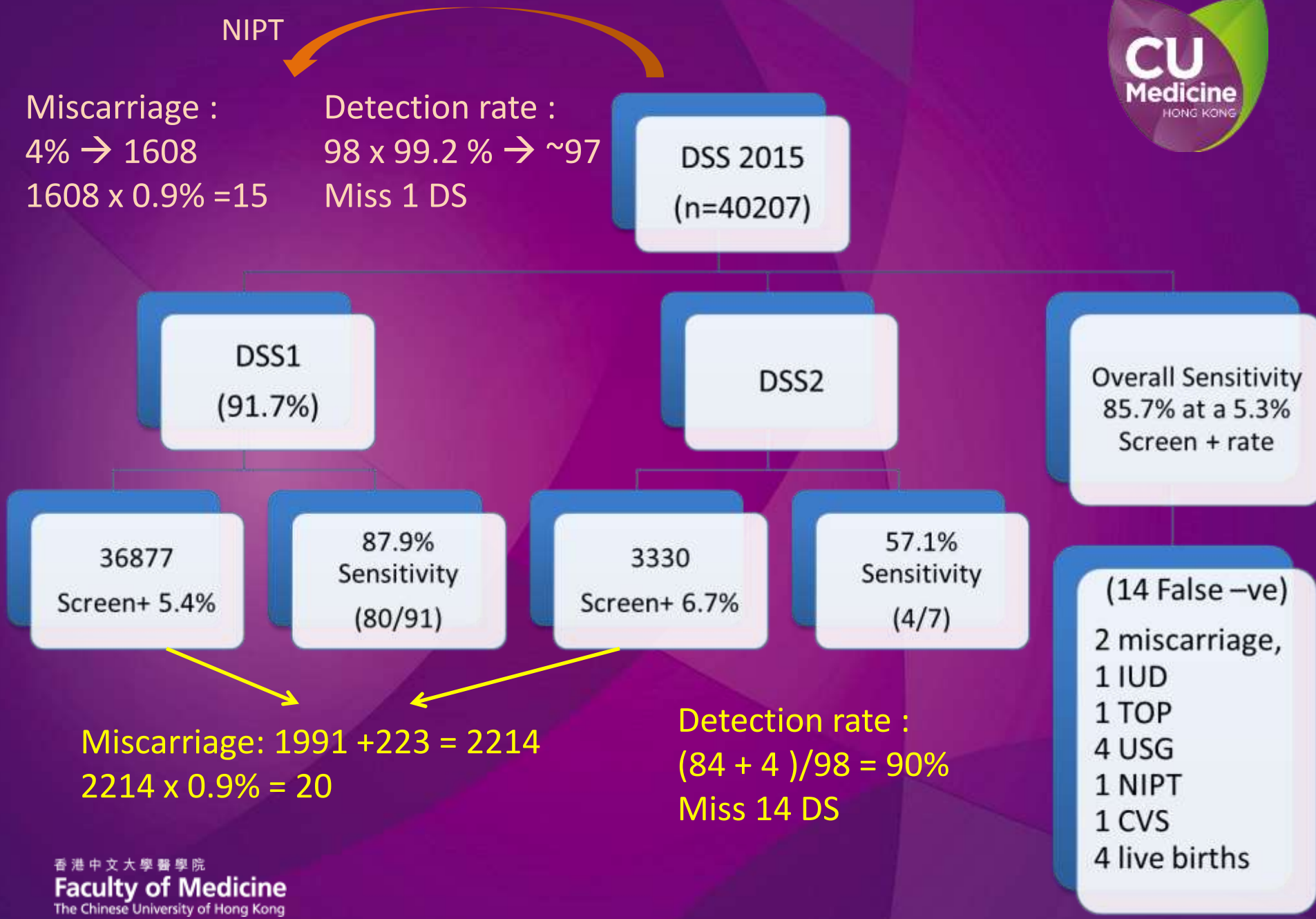
2013

A cost-effectiveness an... ing different strategies to implement noninvasive prenata... wn syndrome screening program

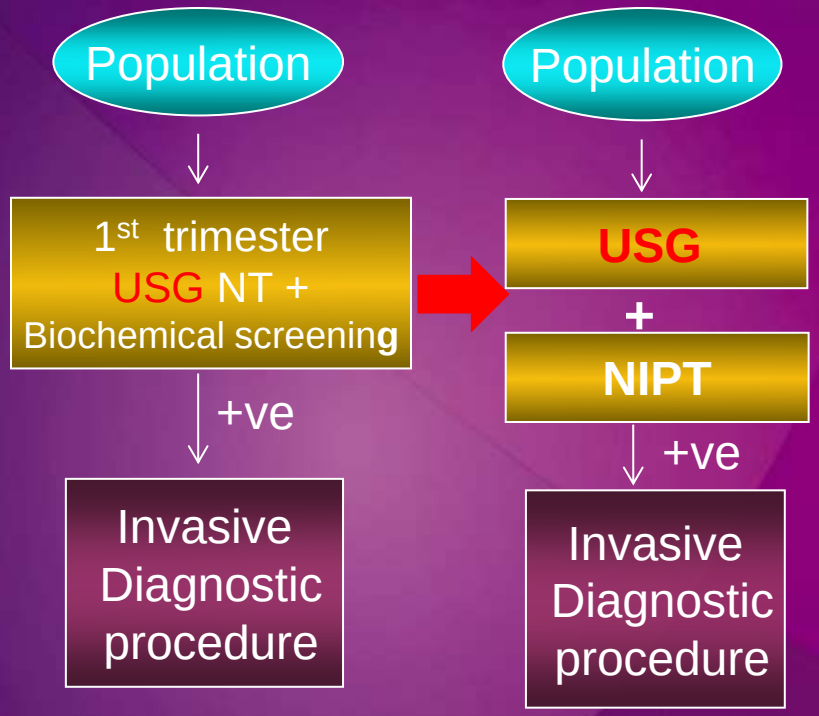
Alice C. AYRES,[1,*] Jennifer A... HITTY[2,...] David A. ELLWOOD[4]

[1]*School of Medicine, Gold Coast Campus, Griffith University, Gold Coast,* [2]*Population and Social Health Research Program, Griffith Health Institute, Centre for Applied Health Economics, School of Medicine, Griffith University, Logan,* [3]*School of Pharmacy, University of Queensland, Brisbane,* [4]*School of Medicine, Griffith University, Gold Coast Campus, Gold Coast, Queensland, Australia*

2014



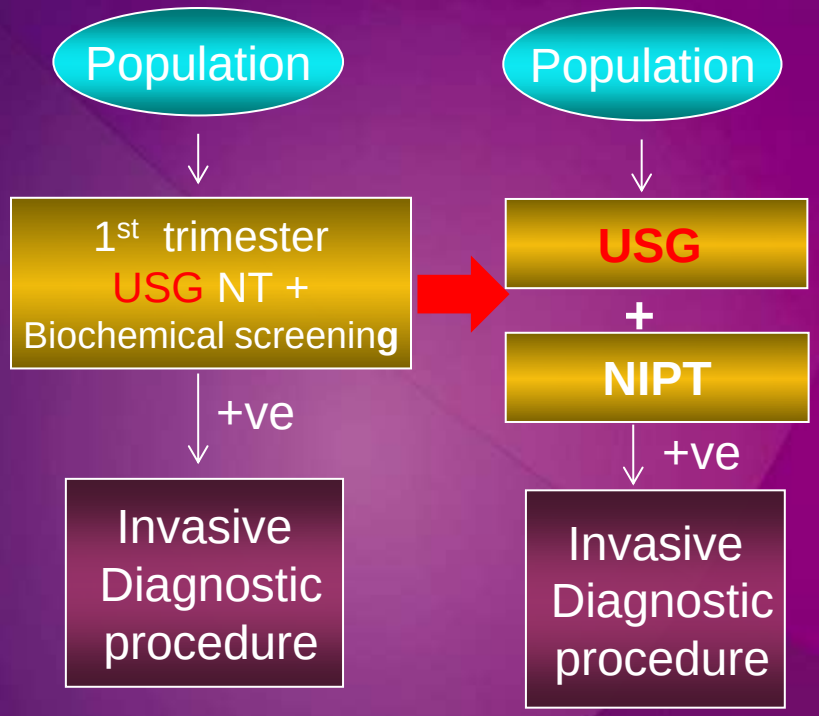
Convert the combined DSS to NIPT



	DSS	NIPT	Per year
USG	Same	Same	
Blood test	HCG+PAPPA ($220) 8.85M	cfDNA ($4400) 177M	~ 168M
Missed DS	14(4)	1	13 (3)
Miscarriage	20	15	-5
Amnio/CVS	2214	1608	-606

Assume NIPT market price : HKD 4400

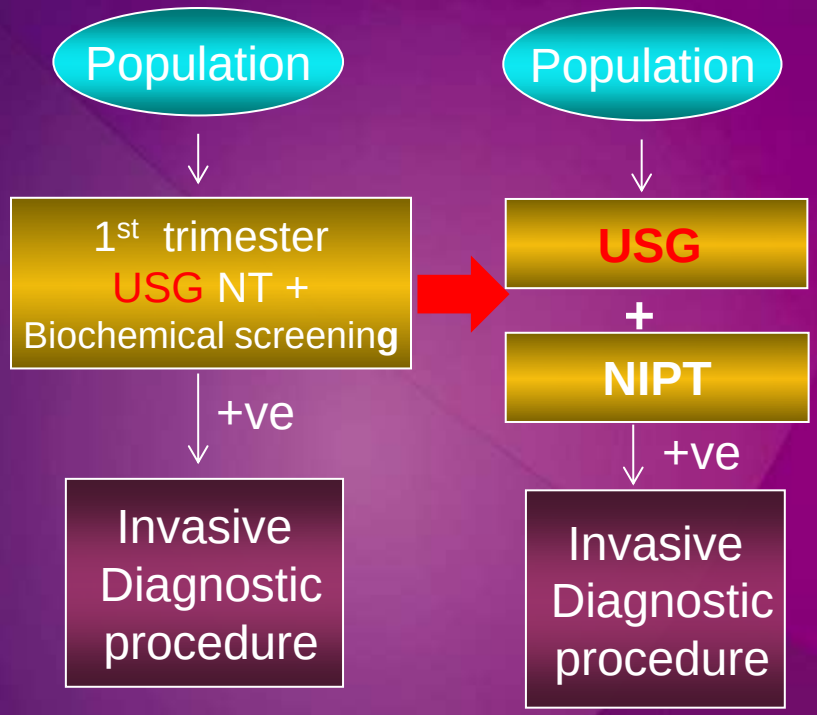
Convert the combined DSS to NIPT



	DSS	NIPT	Per year
USG	Same	Same	
Blood test	HCG+PAPPA ($220) 8.85M	cfDNA ($2200) 88.5M	~ 80M
Missed DS	14(4)	1	13 (3)
Miscarriage	20	15	-5
Amnio/CVS	2214	1608	-606

Assume NIPT market price : HKD 2200

Convert the combined DSS to NIPT



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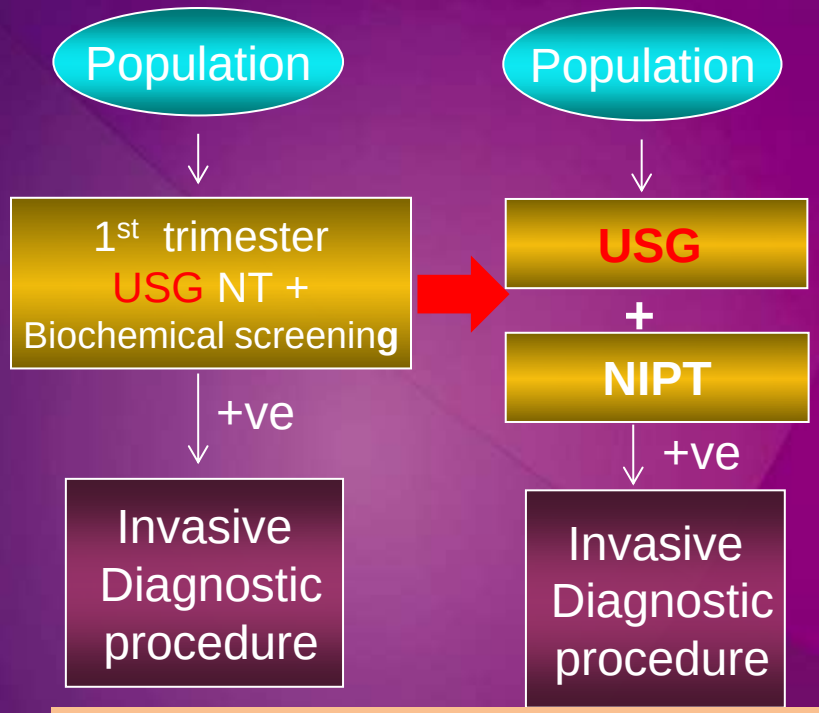
- ? Health and economic costs for every Down's syndrome case
- ? Miscarriage
- Not all family will terminate fetus with DS
- Cost for cffDNA (NIPT) may drop
- IF NIPT provided by HA , number of pregnant women seeking for the services will increase (60000 vs 40000)

Convert the combined DSS to NIPT



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Not for Primary Screening ≠ No role

Cost-effectiveness of NIDT in Practice

Universal Screening - How should it be integrated ?
To reduce iatrogenic loss

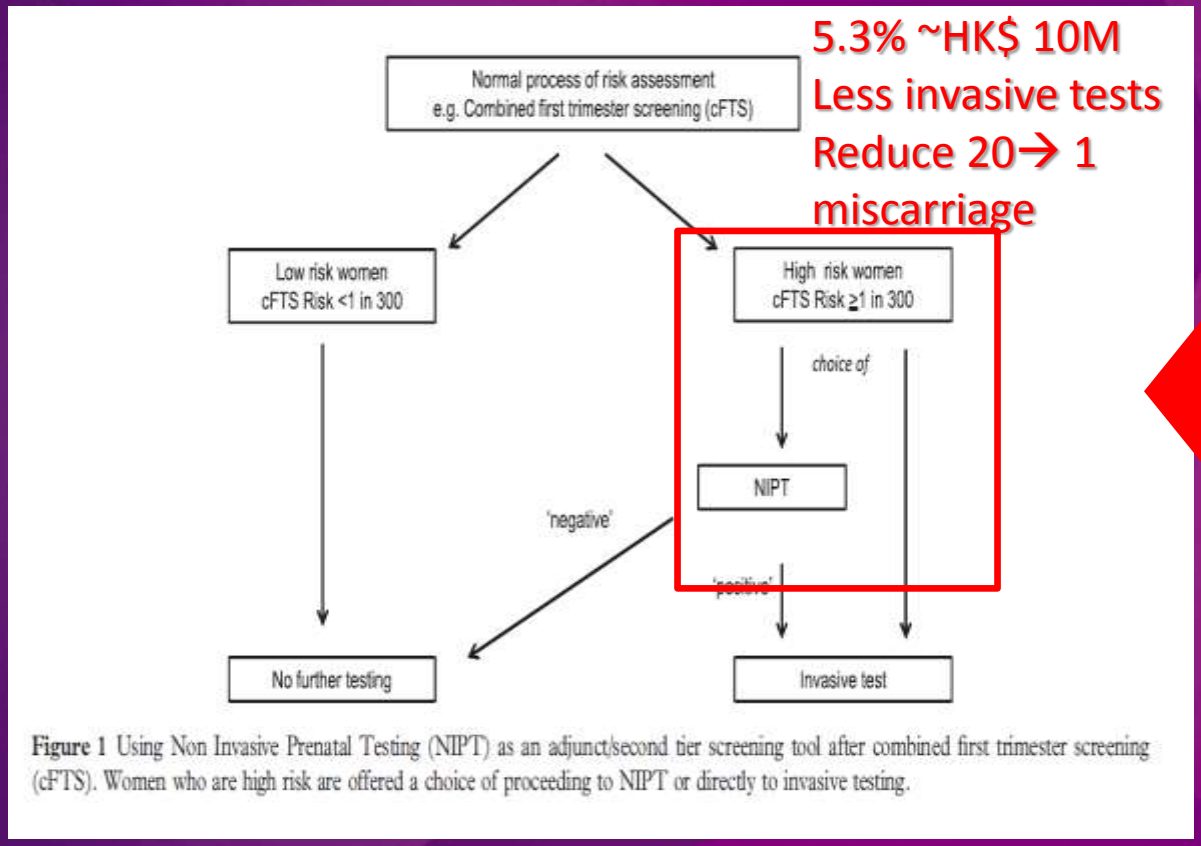
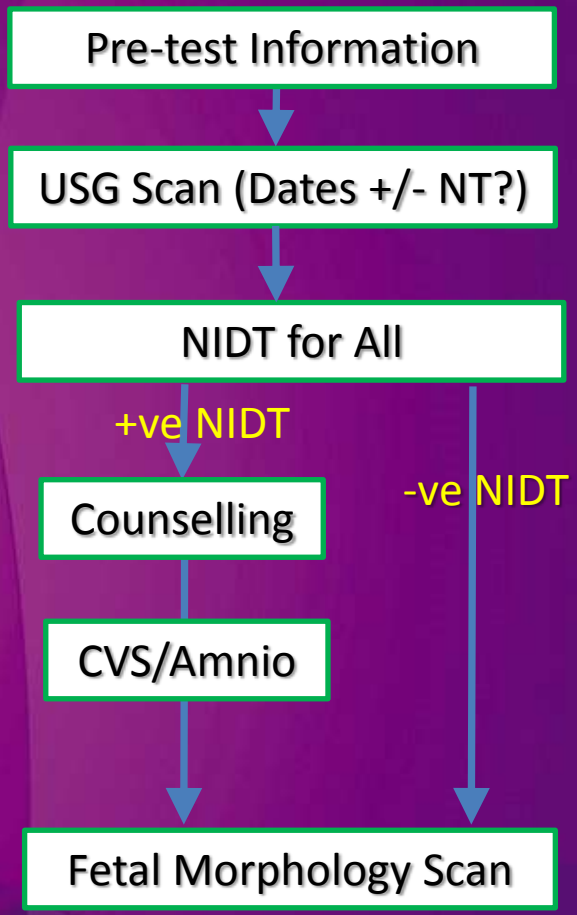


Figure 1 Using Non Invasive Prenatal Testing (NIPT) as an adjunct/second tier screening tool after combined first trimester screening (cFTS). Women who are high risk are offered a choice of proceeding to NIPT or directly to invasive testing.

5.3% ~HK$ 10M
Less invasive tests
Reduce 20→ 1 miscarriage



Cost-effectiveness of NIDT in Practice

Universal Screening - How should it be integrated ?

Why Primary screening ?

Contingent Screening should be more cost-effective

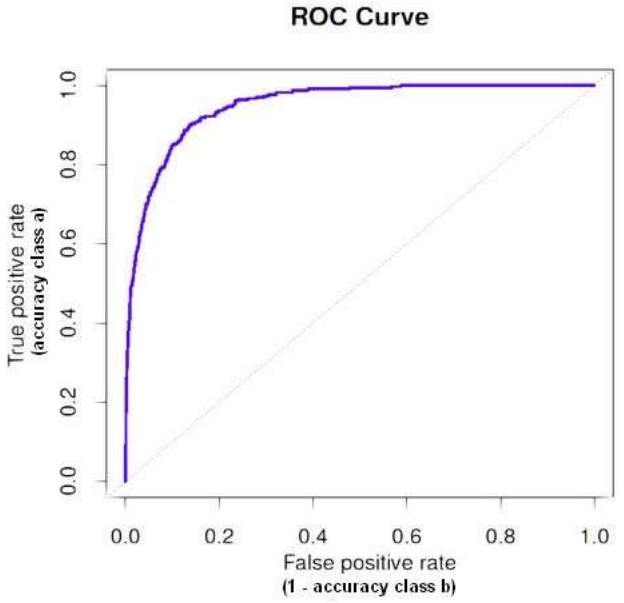
TABLE 2
Projected numbers undergoing noninvasive prenatal diagnosis

Screening			NIPD			
Cut-off (1 in)	DR_S	FPR_S	NIPD	DR_N	FPR_N	TP_N
150	85.0%	2.5%	13,646	99.0%	1.0%	1169
500	94.0%	7%	37,704	99.0%	1.0%	1293
1000	96.0%	12%	60,668	99.0%	1.0%	1320
2000	98.0%	19%	94,103	99.0%	1.0%	1348
5000	99.0%	31%	155,944	99.0%	1.0%	1361
10,000	99.5%	43%	215,785	99.0%	1.0%	1368

250 90% 5%

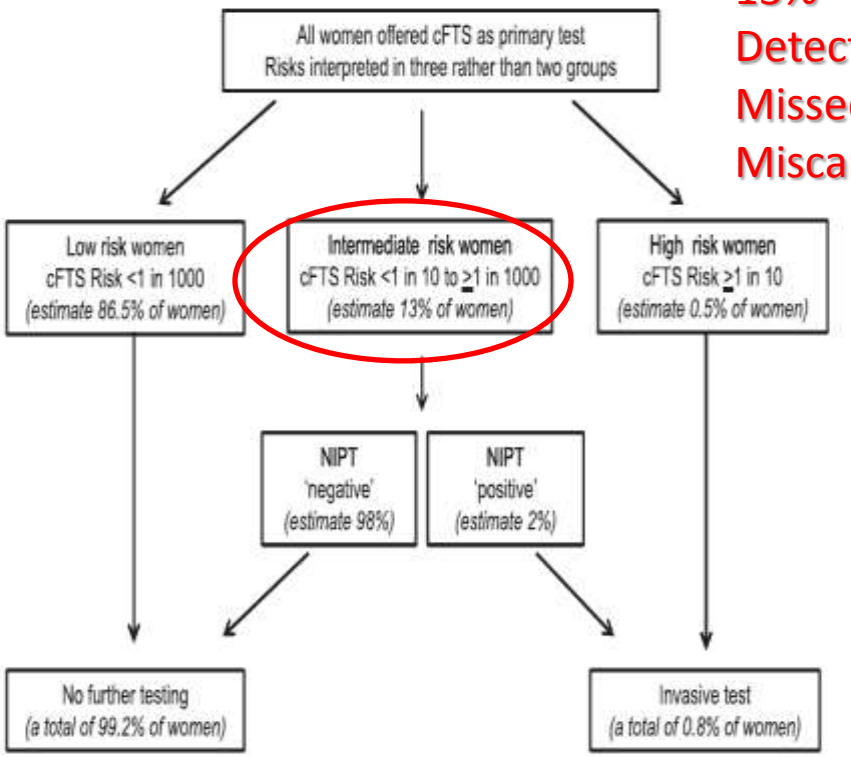
Figures calculated for hypothetical population of 500,000 women. With Down syndrome prevalence at screening of 1 in
rather than NIPD with screening cut-off of 1 in 150, 13,646 women would undergo CVS, detecting 1181 Down syndron
CVS, chorionic villus sampling; DR_N, detection rate with NIPD; DR_S, detection rate with screening; FN_{S+N}, combined fals
prevalence cases – TP_N; FP_N, false-positive results with NIPD; FPR_N, false-positive rate with NIPD; FPR_S, false-positive ra
with NIPD.

Chitty. Noninvasive prenatal testing for aneuploidy. Am J Obstet Gynecol 2012.



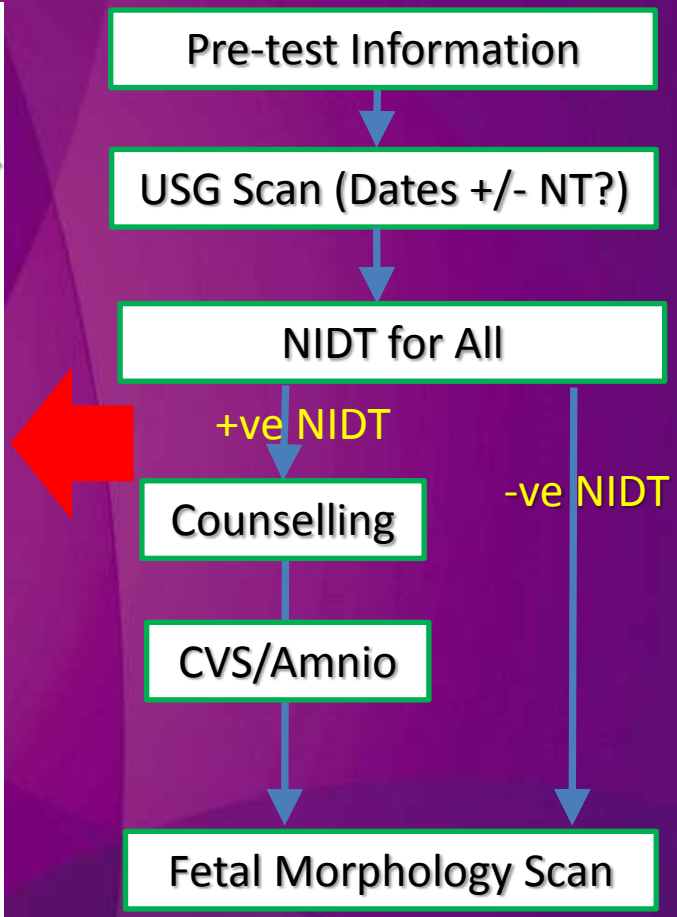
Cost-effectiveness of NIDT in Practice

Universal Screening - How should it be integrated?
To improve detection rate



n alternative 'contingent' model for Non Invasive Prenatal Testing (NIPT) as an adjunct/second tier screening tool after st trimester screening (cFTS).

13% ~HK$ 23M
Detection : 96%
Missed DS: 14 → 4
Miscarriage:20→3



Conclusion

- NIPT should not be used as primary screening for Down's syndrome to replace current combined screening
  - Although detect more Down's syndrome, it will miss other chromosomal/genetic/structural abnormality
  - Retain the first trimester scan will be required to identify these abnormalities
  - The reduction in invasive tests and the procedural related miscarriage is overestimated
  - It is unlikely to be cost-effective

- Services could be improved using NIPT as sequential screening or contingent screening

Thank you