

Is Non-Invasive genetic Prenatal Testing ready for use ?

The evidence, the costs and the ethics
addressed in a HTA with recommendations
for practice and for research

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#HTAiOslo2015



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 Regione Emilia-Romagna


OSLO
HTAI
2015
12th Annual Meeting

Background

Prenatal screening in Emilia-Romagna region

- offered to all pregnant women and
- based on combined test (nuchal translucency + β -HCG + PAPP-A) performed between 10⁺⁰ and 14⁺¹ weeks of gestation

Non Invasive Prenatal Tests (NIPT)

Calculate risk of aneuploidy using cell-free foetal DNA (cffDNA) extracted from maternal blood.

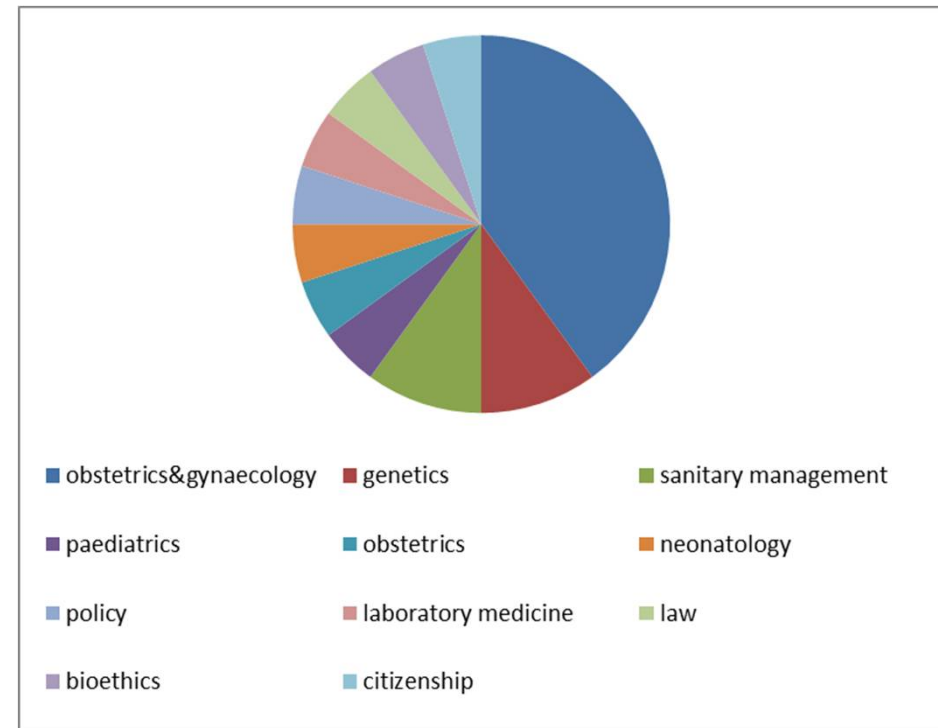
cffDNA is amplified and sequenced (by different techniques)* and risk of aneuploidy elaborated by specific algorithms

* massive parallel sequencing (MPS), targeted sequencing, single nucleotide polymorphisms (SNPs)

**HTA + Recommendations on NIPT
requested by Policy Maker**

Methods – GRADE

- Policy question
- Multidisciplinary panel (n.20)
- Definition of research questions and voting of importance of outcomes (GRADE)
- Literature review + synthesis of results
- 2 rounds of voting for recommendations



+ 7 methodologists

First meeting: Research Questions

Question 1

- NIPT in replacement of Combined test

Question 2

- NIPT in add-on for positive at Combined test (cut off 1/250)

Question 3

- NIPT in add-on for risk 1/1000 - 1/100 at Combined test

Second Meeting: Outcomes

1. Replacement	Vote	2. Add on + (cut off 1/250)	Vote	3. Add on -1/100-1/1000	Vote
True Positive	8	True Positive	8	True Positive	8
False Negative	8	False Negative	8	False Negative	8
True Negative	8	True Negative	8	True Negative	7
False Positive	7	False Positive	8	False Positive	8
↓ Invasive tests	8	↓ Invasive tests	8	↓ Invasive tests	8
↓ miscarriages/adverse events of invasive test	8	↓ miscarriages/adverse events of invasive test	8	↓ miscarriages/adverse events of invasive test	8
↓ % end diagnostic process beyond 15 weeks	8	↑ % end diagnostic process beyond 15 weeks	7	↑ % end diagnostic process beyond 15 weeks	7
↓ anxiety)	6	↑ anxiety	7	↑ anxiety	6
Test failure	4	Test failure	4	Test failure	4
↓ Complexity of diagnostic process	7	↑ Complexity of diagnostic process	7	↑ Complexity of diagnostic process	6
↑ Costs	4,5	↑ Costs	5	↑ Costs	4.5
↓ Costs	4	↓ Costs	4	↓ Costs	4.5

Results: diagnostic accuracy

Q 1

NIPT

Combined test

sensitivity

99.43%
(97.43%-99.87%)

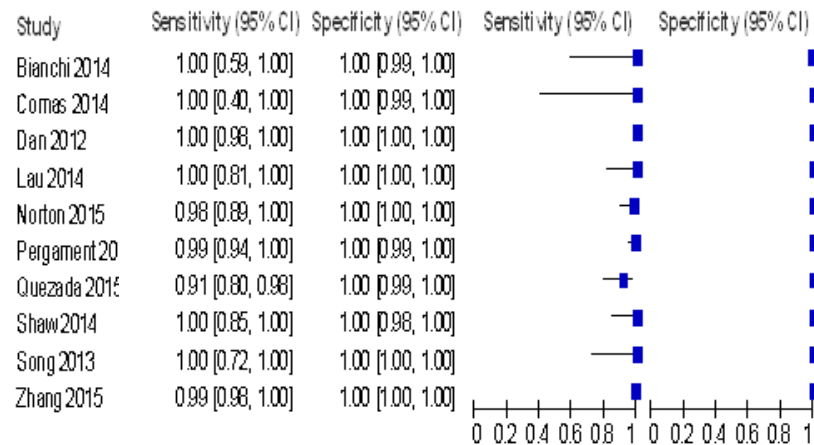
85%

specificity

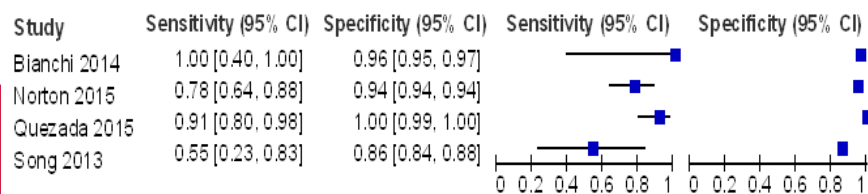
99.91%
(99.80%-99.95%)

95%

NIPT



Combined test



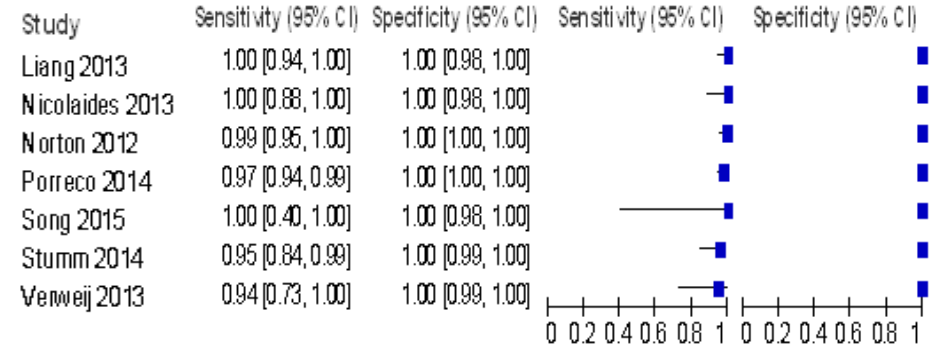
Q2

sensitivity

98.05%
(96.79%-99.31%)

specificity

99.91%
(99.84%-99.98%)

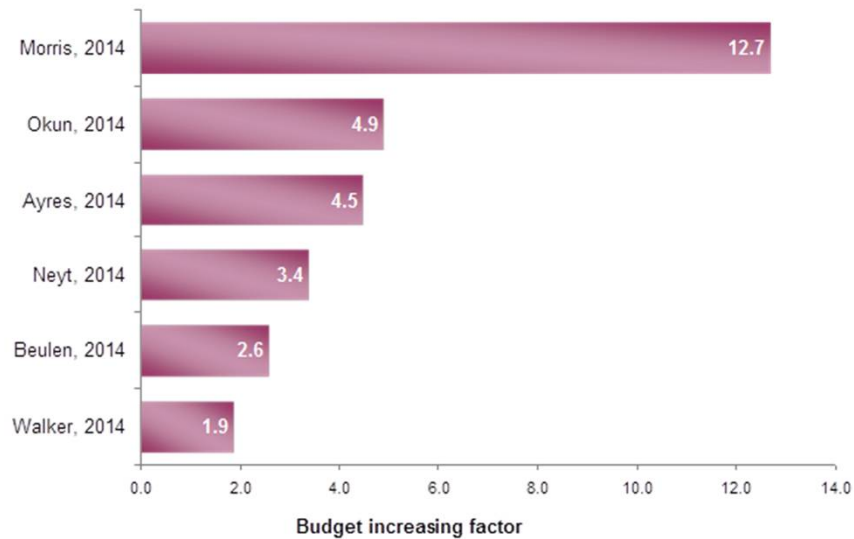


Q3: NO DATA
(studies ongoing)

Q1.Replacement

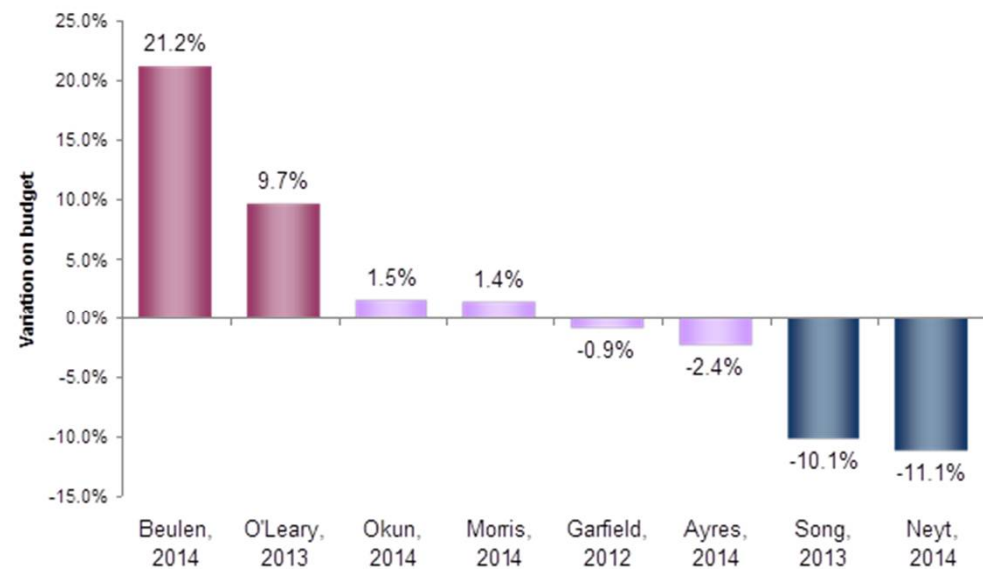
Results : costs

NIPT in Replacement: impact on budget



Q2 . add-on

NIPT in Add-on: impact on budget



Q3: no data

Summary of Findings Q1: replacement NIPT VS CT

Outcome	N of studies	Study design	Limitations	Indirectness	Inconsistency	Imprecision	Reporting bias	Final quality	Effect per 40 000 # NIPT CT	Importance
True Positive	10	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	139 119	CRITICAL
False Negative	10	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	1 21	CRITICAL
True Negative	10	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	39 824 37 867	CRITICAL
False Positive	10	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	36 1993	CRITICAL
Test Failure	10	Cross sectional	Low	Low	None	None	Unlikely	High ⊕⊕⊕⊕	1,5%	IMPORTANT
↓ Invasive tests	1	ITS	High**	-	-	-	-	Very low ⊕	-0,3%	CRITICAL
Costs	6	Comparative	Low	High***	None	High***	Unlikely	Low ⊕⊕	Increase	IMPORTANT
↓ miscarriages/adverse events of invasive test	-	-	-	-	-	-	-	-	-	CRITICAL
↓ % end diagnostic process beyond 15 weeks	-	-	-	-	-	-	-	-	-	CRITICAL
↓ anxiety)	-	-	-	-	-	-	-	-	-	IMPORTANT
↓ Complexity of diagnostic process	-	-	-	-	-	-	-	-	-	CRITICAL

Prevalence 0,349%

* 3 studies with high prevalence of high risk population

** Before and after study reanalysed as ITS

*** High variability in costs

Summary of Findings Q2: NIPT add on

Outcome	N of studies	Study design	Limitations	Indirectness	Inconsistency	Imprecision	Reporting bias	Final quality	Effect per 2112 CT positive #	Importance
True Positive	7	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	117	CRITICAL
False Negative	7	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	2	CRITICAL
True Negative	7	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	1991	CRITICAL
False Positive	7	Cross sectional	Low	Medium*	None	None	Unlikely	Moderate ⊕⊕⊕	2	CRITICAL
Test Failure	7	Cross sectional	Low	Low	None	None	Unlikely	High ⊕⊕⊕⊕	4.6%	IMPORTANT
↓ Invasive tests	1	ITS	High*	-	-	-	-	Very low ⊕	No effect	CRITICAL
Costs	8	Comparative	Low	High ***	Yes	High***	Unlikely	Very Low ⊕	No estimate	IMPORTANT
↓ miscarriages/adverse events of invasive test	-	-	-	-	-	-	-	-	-	CRITICAL
↓ % end diagnostic process beyond 15 weeks	-	-	-	-	-	-	-	-	-	CRITICAL
↓ anxiety)	-	-	-	-	-	-	-	-	-	IMPORTANT
↓ Complexity of diagnostic process	-	-	-	-	-	-	-	-	-	CRITICAL

Prevalence 0,563%

* Mixed definition of target population (high risk)

** Before and after study reanalysed as ITS

*** High variability in costs

Ethics and social context

NIPT vs current practice

Costs

- Public health resources
- Counselling resources/ expertise
- Social equity

Compliance

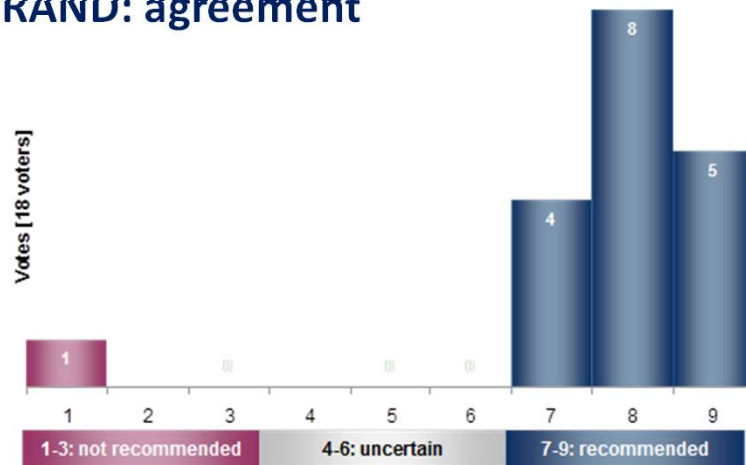
- Reproductive autonomy
- Well being of unborn
- Marginalization of disability

Target disease

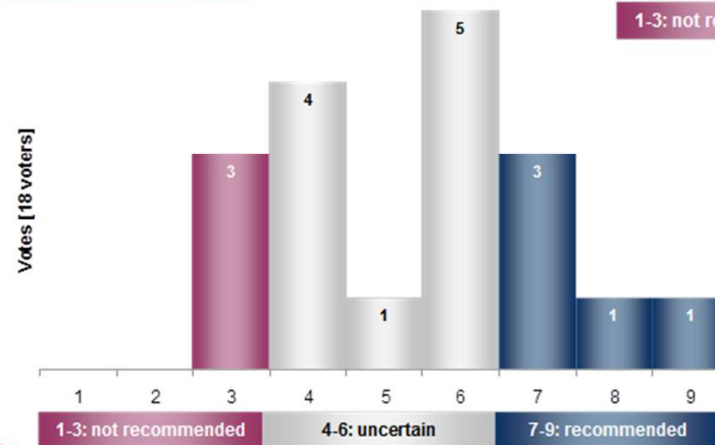
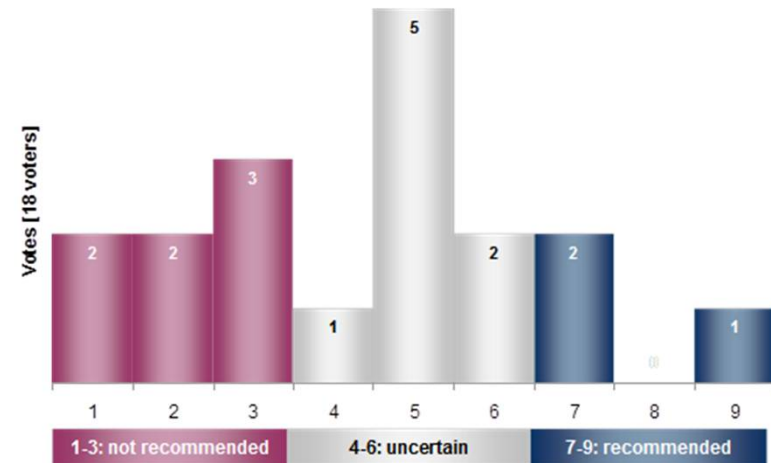
- Relativism disease gravity
- Moral paternalism

Third meeting: first vote

Q1. Replacement: Recommended
median 8
RAND: agreement



Q2. Add-on (a)– median 5
RAND: strong disagreement



Add-on (b)– median 6
RAND: strong disagreement

Combined-Test	
-	+
37 888 (FN 21)	2 112 (FP 1 993)
	↓
	2 112 Invasive test
	119 trisomies

N: 40 000
(140 trisomies)

Q1 Replacement



NIPT	
-	+
39 825 (FN 1)	175 (FP 36)
	↓
	175 Invasive test
	139 trisomies

Combined-Test	
-	+
37 888 (FN 21)	2 112 (FP 1 993)
	↓
	2 112 Invasive test
	119 trisomies

Q2 Add-on



Combined-Test	
-	+
37 888 (FN 21)	2 112 (FP 1 993)
	↓
	NIPT
-	+
1 993 (FN 2)	119 (FP 2)
	↓
	119 Invasive test
	117 trisomies

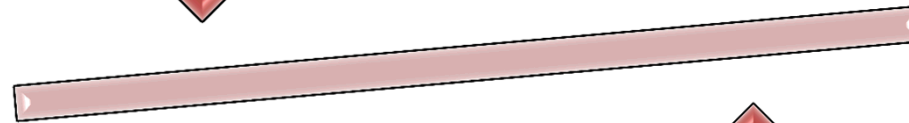
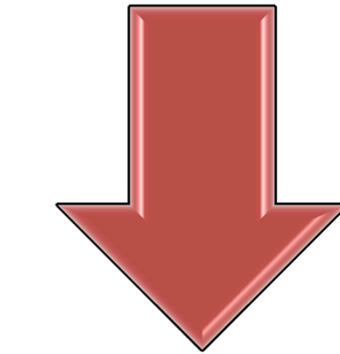
Fourth Meeting

Combined-Test	
-	+
37 888 (FN 21)	2 112 (FP 1 993)
	↓
	2 112 Invasive test
	119 trisomies

Q1 Replacement

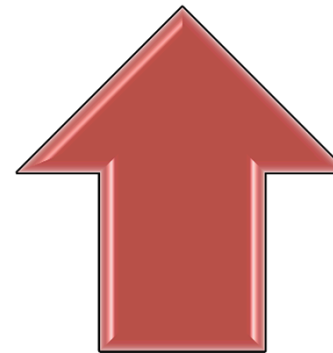
NIPT	
-	+
39 825 (FN 1)	175 (FP 36)
	↓
	175 Invasive test
	139 trisomies

↓ 1957
unnecessary
invasive tests
1 trisomy lost



Combined-Test	
-	+
37 888 (FN 21)	2 112 (FP 1 993)
	↓
	2 112 Invasive test
	119 trisomies

↓ 1991
unnecessary
invasive tests
23 trisomies lost

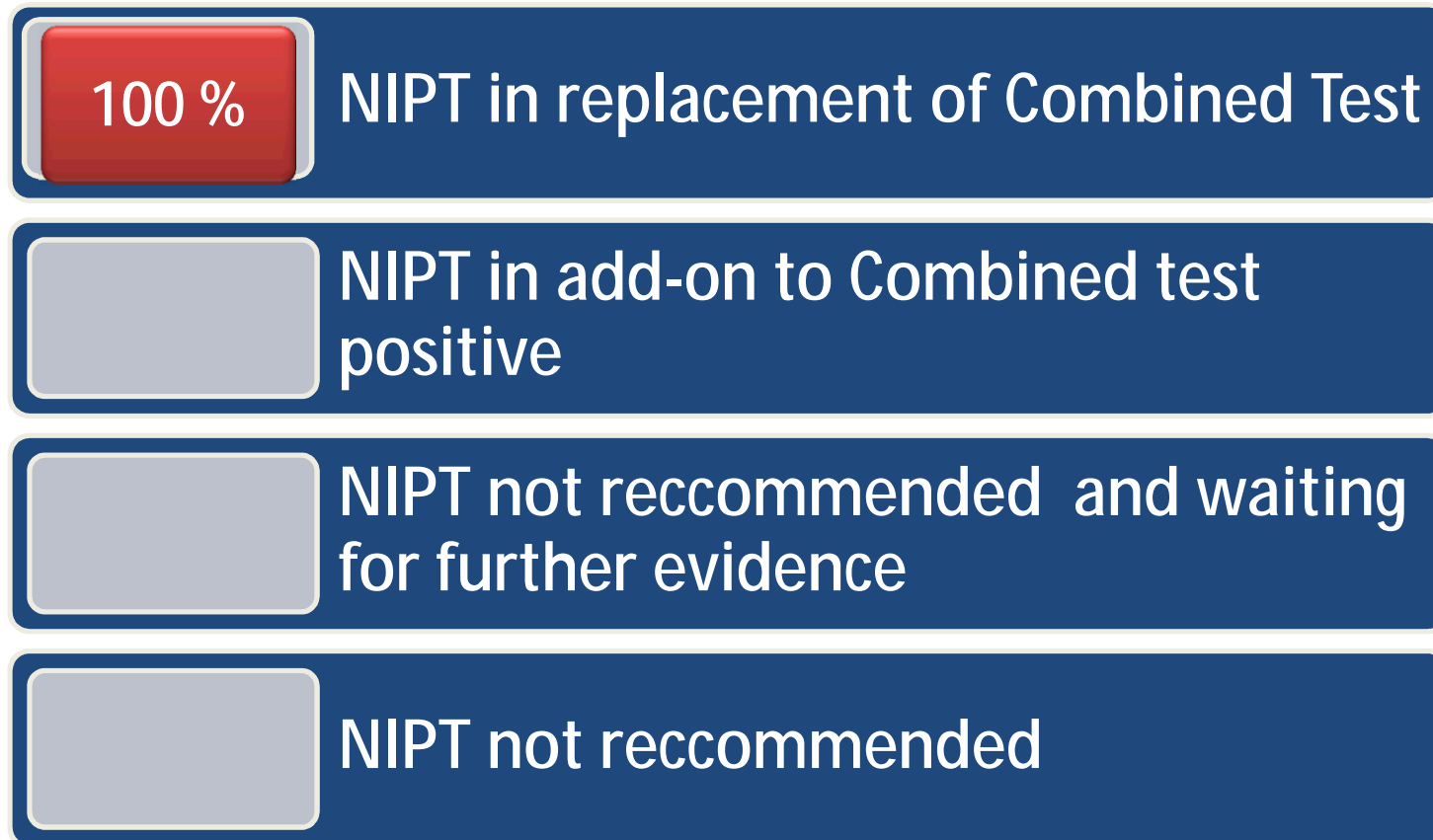


Combined-Test	
-	+
37 888 (FN 21)	2 112 (FP 1 993)
	↓
	NIPT
	↓
	119 Invasive test
	117 trisomies

Q2 Add-on

Fourth Meeting

Fourth meeting: Second Vote



Conclusions



- Rapid response to Policy question
- Transparent and scientific method
- Consensus from a multidisciplinary panel

<http://assr.regione.emilia-romagna.it>

Thank you