LBC IN CERVICAL CANCER PRECURSORS SCREENING: a report of HEALTH TECHNOLOGY ASSESSMENT

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INDICE

CHAPTER 1. INTRODUCTION

1.4 Aim of the report

Aim of this report is to evaluate
the impact of the introduction of liquid-based cytology
in cervical screening regarding
efficacy, adverse effects, costs and organizative impact.

CHAPTER 2. EFFICACY AND ADVERSE EFFECTS

Efficacy

- An increase of transversal sensitivity for CIN 2+ is necessary to increase efficacy in order to prevent invasive cancers.

- In cervical screening, a major reduction of CIN 3 at the second round of screening in the arm screened by the experimental method is considered as an accetable increase of efficacy in preventing invasive cancers .

- It is necessary to perform controlled and randomized trials (RCT) through two rounds of screening.

Results

Transversal accuracy

Trial NTCC

relative sensitivity is 1.17 and 1.03 hystologic endpoint CIN 2+
cytologic cut-off ASCUS and LSIL

relative sensitivity is 0.84 and 0.72 hystologic endpoint CIN 3+
cytologic cut-off ASCUS and LSIL

decrease of PPV

Abruzzo randomized study

DR of CIN 2+ 0.54% CC 0.66% LBC

PPV very similar in both two arms

NETHCON study

No significative differences concerning DR and PPV

All the RCT used ThinPrep

Adverse effects

Recall for repetition, due to unsatisfactory cytology

Referral to unnecessary colposcopies (decrease of PPV)

Increased overdiagnoses of CIN which would regress spontaneously (increase of cumulative DR on two rounds of screening)

Methods

The considered studies compare manually read CC to manually read LBC

- **Transversal accuracy**

- **Longitudinal studies**

Articles about RCT have been examinated to verify if they included data concerning more rounds of screening

- **Rate of unsatisfactory cytologies**

Meta-analysis (Davey et al. 2006)

RCT (successively published)

Transversal accuracy

Several studies

Dissimilar conclusions

Problems about the quality of the studies
(comparability between the two methods, the considered endpoint and problems about the final examination)

Systematic review (Davey 2006) settles that randomized trials are necessary

Transversal accuracy

- Meta-analysis (Arbyn et al. 2008) considers studies in which all tested women➔colposcopy or RCT in which all positive➔colposcopy
- Italian trial NTCC (Ronco et al. 2007) performed in 6 Regions
  45174 randomized women, invited for screening
- Abruzzo study (Maccallini et al.2008) 8654 randomized women
- Dutch study NETHCON (Siebers et al.2009) 89784 randomized women

Longitudinal studies

No RCT performed through at least 2 rounds of screening

Rate of unsatisfactory cytologies

Meta-analysis Davey: considerable heterogeneity among studies

-0,14% difference between % of unsatisfactory LBC and CC

NTCC:	unsatisfactory LBC 2.59%	unsatisfactory CC 4.10%
Abruzzo:	unsatisfactory LBC 1.3%	unsatisfactory CC 4.3%
NETHCON:	unsatisfactory LBC 0.33%	unsatisfactory CC 1.11%

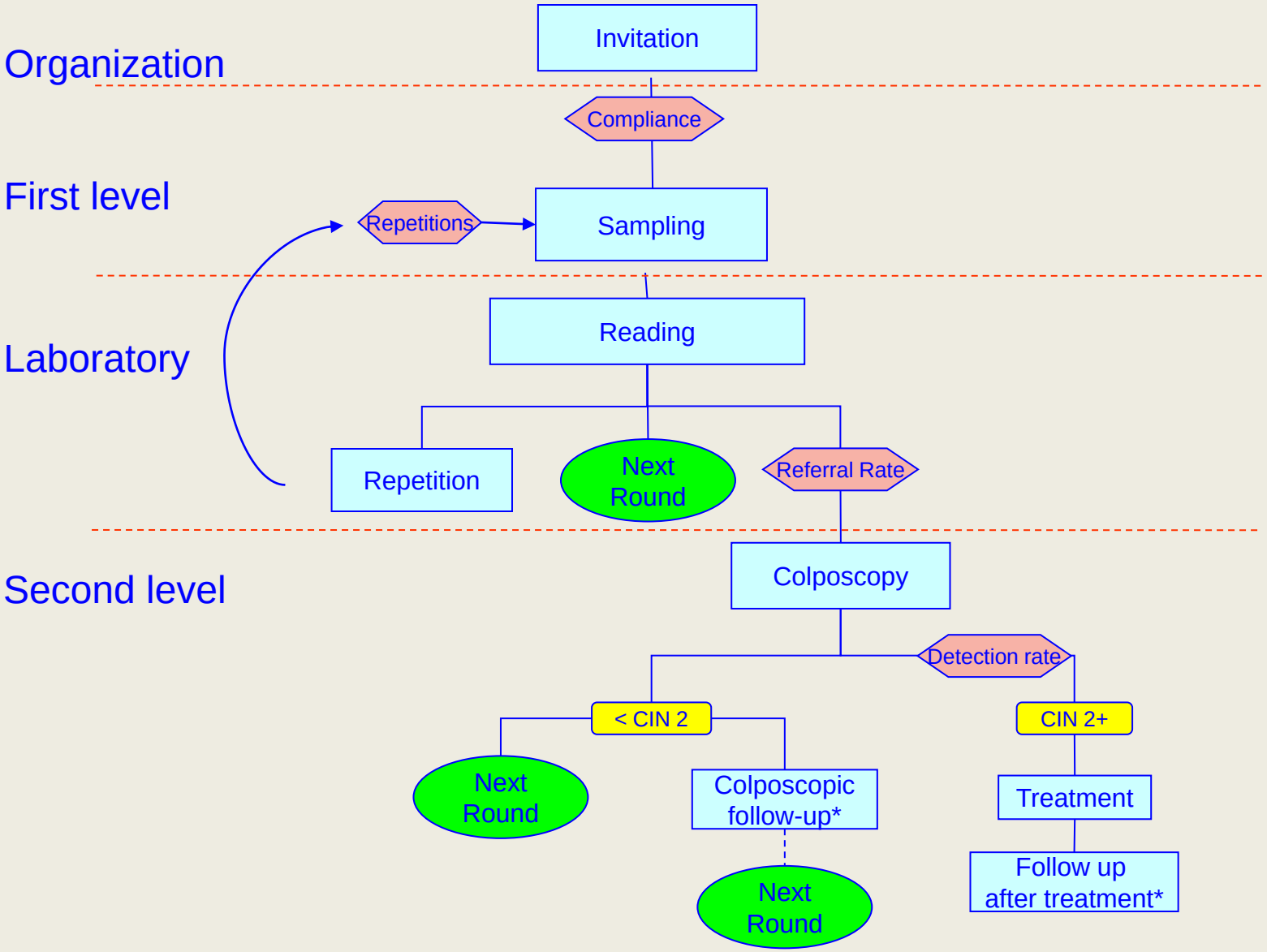
- LBC and CC have the same transversal sensitivity
- LBC reduces the rate of unsatisfactory cytologies
- Available data don’t permit us to conclude that LBC screening is different, regarding efficacy and adverse effects, from CC screening

Economic evaluation - Methods

- Identification of the **screening protocol** (both CC and LBC)

- Identification of the **single differences** caused by the two different methods

The screening protocol



Economic evaluation - Methods

- The only differences individuated in the procedure concern laboratory (preparation of the slide).

→ **No changement perceived from women.**

→ **A few changements perceived from midwives and gynecologists.**

Economic evaluation - Methods

- Collection of the parameters of compliance and epidemiologic (**repetitions, referral rate**, **number of colposcopies**)

- Recognition of **the real costs** of every single service which constitutes the process of screening (organization, sampling, laboratory, second level)

Parameters of conventional cytology

	Benchmark	Min	Max
Compliance CC and LBC	40%	20%	80%
Mean value of citologies for screened woman	1.052	1.012	1.121
Laboratory and reading cost	12.15€	11.00€	15.50€
Referral Rate to colposcopy	3.8%	1.0%	4.4%
No of colposcopies FU conventional	2.2	1.3	2.5

Parameters of liquid based cytology

	Benchmark	Min	Max
Compliance CC and LBC	40%	20%	80%
Mean value of citologies for screened woman	1.037	1.011	1.085
Cost of the vial	6.00 €	5.00 €	7.00€
Cost for LBC processing	0.40 €	0.30 €	0.90 €
Laboratory and reading cost	9.77 €	7.30 €	13.13€
Referral Rate to colposcopy	6.3%	1.7%	7.3%
No of colposcopies FU conventional	2.2	1.3	2.5

LBC Reading cost

Analysis items

- Cost noticed in a laboratory where screening is performed by technical personnel and with great volume of activity
- Less screening time (saving 20%-50%)
- Different workloads have been supposed

Economic evaluation - Methods

Statement of the fixed and variable parameters in a simple model inclusive of all the steps of the process of screening, in order to obtain the total cost for screened woman.

Cost of a round of screening – Conventional cytology

	Parameter		No	Unit cost	Total cost
Invitation			25,000	€ 3.00	€ 75,000.00
Complying women	Compliance	40.0%	10,000		
Sampling (including repetitions)		1.052	10,520	€ 6.84	€ 71,956.80
Laboratory and reading			10,520	€ 12.15	€ 127,818.00
Women referred to colposcopy	RR	3.8%	381		
Total colposcopies (immediate and FU)		2.2	837	€ 95.00	€ 79,540.19
Total cost				**€ 35.43**	€ 354,314.99

Cost of a round of screening – LBC (Thin Prep)

	Parameter		No	Unit cost	Total cost
Invitation			25,000	€ 3.00	€ 75,000.00
Complying women	Compliance	40.0%	10,000		
Sampling (including repetitions)		1.037	10,370	€ 12.78	€ 132,528.60
Thin Prep slide preparation			10,370	€ 0.40	€ 4,148.00
Laboratory and reading cost			10,370	€ 9.77	€ 101,314.90
Women referred to colposcopy	RR	6.3%	631		
Total colposcopies (immediate and FU)		2.2	1,389	€ 95.00	€ 131,982.56
Total cost				**€ 44.50**	€ 444,974.06

Sensitivity analysis

- Variable parameters have been implemented, varying them one at a time.

- Two extreme scenery have been identified.

One has implemented all the minimizing variants,

the other the maximizing ones.

Compliance kept constant (40%).

Minimum and maximum costs for one round of screening				
Variable parameter	Conventional		LBC	
	Benchmark € 35.43		Benchmark € 44.50	
	Min Cost	Max cost	Min cost	Max cost
Compliance	€ 31.68	€ 42.93	€ 40.75	€ 52.00
Mean number citologies for screened woman	€ 34.67	€ 36.74	€ 43.90	€ 45.60
Vial Thin Prep			€ 43.46	€ 45.53
LBC processing			€ 44.39	€ 45.02
Laboratory and reading	€ 34.22	€ 38.96	€ 41.94	€ 47.98
Referral Rate to colposcopy	€ 29.57	€ 36.67	€ 34.85	€ 46.56
No of colposcopies (conventional FU)	€ 32.18	€ 36.52	€ 39.10	€ 46.30
Extreme scenery (compliance 40%)	€ 26.79	€ 42.99	€ 29.19	€ 55.01

Conclusions

From the economic point of view,

if the described variables are applied,

LBC screening appears to be too expensive

compared to conventional cytology.

Looking to the future…..

- **HPV testing could be introduced as primary screening in the near future:**

Reading slides would be necessary only for the 5-7% of the screened women, but the cost of the vials would be applied on the women at all: ***too expensive!!!***

- **It's desiderable that industries**

develop specimen collection and transport devices which allow molecular testing and cytology on the same material, without additional treatments and ***at bargain prices!!!***

CHAPTER 4. ORGANIZATIVE AND ETHYCAL IMPACT

Organizative aspects

are poorly documented in literature

reflect the specific and different national situations

It's difficult to transfer data from foreign experiences to Italian situation

"This chapter is based on a reasoned investigation of organizative and ethycal problems of Italian situation"

Sampling

- No difference between LBC and CC
- Very small training of providers
- More difficulty in transporting vials instead of slides

- LBC can be used for molecular testing

  (ASC-US or LSIL Triage by HPV testing and Cytologic triage of HPV positive women)

We don't have to call women again

We can spare the possible loss at follow-up and relative cost

But……..

The cost of the equipments is applied on women at all, meanwhile double testing concerns only a few of them

Triage by HPV testing about 3%, Cytologic triage about 7%

A conversion phase is necessary before HC2 HPV test from LBC specimens

manual conversion: cost, decreased reproducibility

automatized conversion is possible, but we haven't enough data

Preparation and reading of cytology

Costs, organization and quality strongly suggest to centralize cytologic reading, conventional cytology too,

in the case of LBC the costs suggest that

centralization is more than ever necessary

Taking LBC could be an approach to solve the problem of the decrease of cytologists in Italy, *altough alternative solutions as automation-assisted reading and HPV test as primary screening have to be considered*

- Initial period of training is necessary

- Quality assurance currently applied in Italian screening programmes needn’t substantial changements

Dicunt, tradunt, ferunt…

After an initial period of adaptation,

LBC is pleasant

for most cytologists

Computer-assisted screening

LBC can be coupled to computer-assisted reading

Some italian and foreign studies have estimated its sensitivity

Ethycal and legal impact and communication

In comparison to CC, LBC doesn't modify ethycal, legal and communicative problems, as the differences between the two methods concern preparation and reading of cytology, not the other aspects of screening

CONCLUSIONS

There is no evidence at the moment that LBC

- increase the sensitivity of the cytologic test
- increase efficacy of screening in preventing invasive cancers

There is evidence that LBC

- decreases the rate of unsatisfactory cytologies
- permits to reduce screening time
- can be used for molecular testing without recalling women

Nevertheless, in Italian situation, savings derived from all this are not sufficient to counterbalance the greater costs due to the prices applied by the producers at the moment .

My personal conclusions

- I think this report is very well-reasoned and weighed
- I think this report is politically correct

- I hope to have respected the purposes of The Working Group

- I hope my English is fairly comprehensible for Philip Castle

I thank you all for the attention