

Uso del self-sampler per aumentare la compliance allo screening cervicale: revisione sistematica degli studi

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Background

La maggior parte dei cancro invasivi nei paesi industrializzati si verifica in quella piccola parte della popolazione che non ha mai effettuato Pap test o lo effettua saltuariamente.

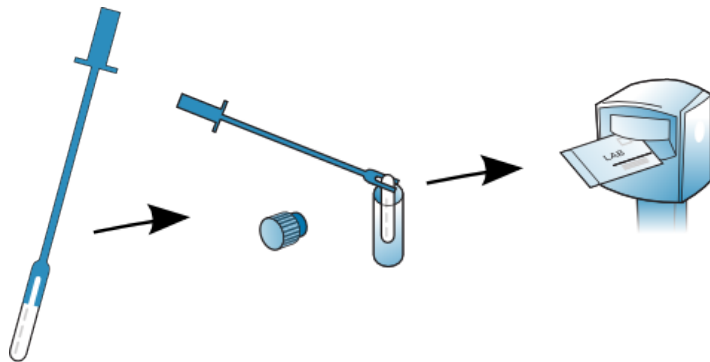
Chiara evidenza scientifica che uno screening con **test clinicamente validati** per il DNA di HPV oncogeni come test di screening primario e **con un protocollo appropriato**, è **più efficace** dello screening basato sulla citologia

Background

Il test HPV si può effettuare su campioni autoprelevati in fase liquida.



Graphic: Internet



GISCI

Validazione clinica: self-samples versus cytology on clinician-collected samples to detect CIN2+

Study	Participants and setting	Reference standard	HPV test	Method (self vs clinician)	Sensitivity ** %	Specificity ** %	PPV %	NPV %
Wright et al. (2000)(31)	1385 Healthy subjects (community)	Colposcopy (all women with abnormal results of any screening tests)	HR HC2	Dacron swab vs conventional cytology: 1. ≥ASCUS 2. ≥LSIL	Self: 86.1 Clin 1: 87.9 Clin 2: 80.7	Self: 81.4* Clin 1: 86.4* Clin 2: 95.9*	Self: 13.2* Clin 1: 17.8* Clin 2: 39.1*	Self: 98.2* Clin 1: 98.4* Clin 2: 98.3*
Belinson et al. (2001)(34)	1997 Healthy subjects (community)	Colposcopy (all women)	HR HC2	Dacron swab vs liquid based cytology	Self: 82.6	Self: 85.9	Self: 20.9 1: 16.0 2: 37.9	Self: 99.1 Clin 1: 99.7 Clin 2: 99.4
Belinson et al. (2003)(33)	8497 Healthy subjects (community)						15.1* 1: 17.9* 2: 34.6*	Self: 99.3* Clin 1: 99.3* Clin 2: 98.9*
Salmeron et al. (2003)(32)	7732 Healthy subjects (screening programme)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Cotton Dacron swab vs conventional cytology	Self: 71.3 Clin: 59.4	Self: 89.2 Clin: 98.3	Self: 9.1 Clin: 36.1	Self: 99.6 Clin: 99.5
Brink et al. (2006)(27)	64 Symptomatic women and 32 healthy volunteers (gynaecological clinic)	Colposcopy (all referred women and the volunteers)	HR GP 5+/6+ PCR	Cervico-vaginal lavage vs liquid based cytology	Self: 91.9 Clinic: 83.8 P= 0.5	Self: 45.6* Clinic: 50.0*	Self: 52.3* Clinic: 51.7*	Self: 99.7* Clinic: 92.9*
Szarewski et al. (2007)(37)	920 Healthy subjects (screening programme or family planning clinic)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Cotton swab vs conventional cytology	Self: 81.0 Clin: 81.0	Self: 82.0 Clin: 96.2	Self: 9.5 Clin: 33.3	Self: 99.7 Clin: 99.5
Bhatla et al. (2009)(38)	546 Symptomatic women (gynaecological clinic)	Colposcopy (all women)	HR HC2 and PGMY09/11 PCR	Vaginal brush vs conventional cytology: 1. ≥ASCUS 2. ≥LSIL	HC2 Self: 80.0 PCR Self: 82.5 Clin 1: 77.5 Clin 2: 70.0	HC2 Self: 88.1 PCR Self: 93.6 Clin 1: 87.3 Clin 2: 94.7	HC2 Self: 36.4 PCR Self: 52.4 Clin 1: 34.1 Clin 2: 52.8	HC2 Self: 98.1 PCR Self: 98.4 Clin 1: 97.9 Clin 2: 97.4
Dijkstra et al. (2012)(39)	135 symptomatic women	Colposcopy (all women)	HR GP 5+/6+ PCR	Vaginal brush vs liquid based cytology	Self: 93.0 Clin: 90.7	Self: 51.1 Clin: 28.3	Self: 37.1* Clin: 47.1*	Self: 96.7* Clin: 94.0*

Sensibilità: uguale o maggiore
Specificità: minore

Validazione clinica: HPV on self-samples versus clinician-collected samples to detect CIN2+ (screening)

Study	Participants and setting	Reference standard	HPV test	Method (self vs clinician)	Sensitivity** %	Specificity** %	PPV %	NPV %
Wright et al. (2000)(31)#	1385 healthy subjects (community)	Colposcopy (all women with abnormal results on any tests)	HR HC2	Vaginal swab vs cervical brush	Self: 66 Clin: 84 P=0.01	Self: 81 Clin: 83	Self: 13 Clin: 17	Self: 98 Clin: 99
Sellors et al. (2000)(53)#	200 healthy subjects (colposcopy clinic)	Colposcopy (all women)	HR HC2	Vaginal (1), vulvar swab (2), urin specimen (3) vs cervical brush	Self (1): 86 Self (2): 62 Self (3): 45 Clin: 98	Self (1): 54 Self (2): 63 Self (3): 70 Clin: 52	Self (1): 43 Self (2): 40 Self (3): 38 Clin: 46	Self (1): 91 Self (2): 80 Self (3): 76 Clin: 99
Belinson et al. (2001)(34)#	1997 healthy subjects (community)	Colposcopy (all women)	HR HC2	Vaginal swab vs cervical brush	Self: 83 Clin: 95	Self: 86 Clin: 85	Self: 21 Clin: 23	Self: 99 Clin: 100
Lorenzato et al. (2002)(46)#	253 high-risk population (screening programme)	Colposcopy (all women)	HR HC2	Vaginal swab vs cervical brush	Self: 50 Clin: 75 P value < 0.03	Self: 86 Clin: 88	Self: 53 Clin: 69	Self: 82 Clin: 91
Belinson et al. (2003)(33)#	8497 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	HR HC2	Vaginal vs cervical brush	Self: 88 Clin: 97	Self: 77 Clin: 88	Self: 15 Clin: 18	Self: 99 Clin: 100
Salmeron et al. (2003)(32)#	773 (scr)							Self: 100 Clin: 100
Holanda et al. (2006)(11)	878 (scr)							NR
Szarewski et al. (2007)(37)	920 (scr)							Self: 99 Clin: 100
	screening programme family planning clinic					significant)		
Qiao et al. (2008)(12)	2530 healthy subjects (community)	Colposcopy (all women)	careHPV	Vaginal vs cervical brush	Self: 72.9 Clin: 84.3 P value: 0.06 (AUC ROC curve)	Self: 87.7 Clin: 87.5 P value: 0.06 (AUC ROC curve)	Self: 15.1 Clin: 16.9	Self: 99.1 Clin: 99.5
Belinson et al. (2010)(36)	2625 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	HC2	Vaginal vs cervical brush	Self: 80.9 Clin: 97.9 P=0.008	Self: 88.6 Clin: 90.2 P=0.001	Self: 11.4* Clin: 15.4*	Self: 99.6* Clin: 100.0*
Belinson et al. (2011)(47)§	8556 healthy subjects (community)	Colposcopy (all women with abnormal HPV and/or cytology results)	Cervista and MALDI-TOF assay	Vaginal sample (POI/NIH or brush) vs cervical brush	Cervista Self: 70.9 Clin: 95.0 P=0.0001 MALDI-TOF Self: 94.3 Clin: 94.3 P=1.0	Cervista Self: 86.1 Clin: 90.3 P<0.001 MALDI-TOF Self: 87.6* Clin: 89.4 P<0.001	Cervista Self: 7.9* Clin: 14.1* MALDI-TOF Self: 11.3* Clin: 13.0*	Cervista Self: 99.4* Clin: 99.9* MALDI-TOF Self: 99.9* Clin: 99.9*

Sensibilità: minore (due studi uguale)

Specificità: minore

Validazione clinica: HPV on self-samples versus clinician-collected samples to detect CIN2+ (referral population)

Study	Participants and setting	Reference standard	HPV test	Method (self vs clinician)	Sensitivity** %	Specificity** %	PPV %	NPV %
Morrison et al. (1992)(44)#	17 evaluated for abnormal cytology (colposcopy clinic)	Colposcopy (all women)	PCR (11 types)	Lavage vs lavage	Self: 100 Clin: 100	Self: 14 Clin: 29	Self: 54 Clin: 58	Self: 100 Clin: 100
Hillemanns et al. (1999) (43)	247 high-risk population (colposcopy clinic)	Colposcopy (all women)	HR HC2	Vaginal vs cervical brush	Self: 92 Clin: 92 (NS)	Self: NR Clin: NR	Self: NR Clin: NR	Self: NR Clin: NR
Nobbenhuis et al. (2002)(26)#	71 women evaluated for abnormal cytology (colposcopy clinic)	Colposcopy (all women)	HR GP5+/6+-PCR	Lavage vs cervical brush	Self: 81 Clin: 91	Self: 88 Clin: 43	Self: 70 Clin: 58	Self: 79 Clin: 84
Garcia et al. (2003)(23)#	334 women*	Colposcopy (all women)	PGMY09/11 PCR	Vaginal brush vs. cervical brush	Self: 49 Clin: 82	Self: 73 Clin: 67	Self: 44 Clin: 52	Self: 77 Clin: 90
Geo et al. (2006)(42)§							Self: 41.3 Clin: 42.1	Self: 84.6 Clin: 83.3
Daponte et al. (2006)(54)							Self: 82.9 Clin: 88.1	Self: 70.2 Clin: 73.9
Brink et al. (2006)(27)							Self: 52* Clin: 55*	Self: 90* Clin: 93*
Bhatia et al. (2009)(38)	548 symptomatic women (gynecological clinic)	Colposcopy (all women)	HR HC2 and PGMY09/11 PCR	Vaginal vs cervical brush (PCR or HC2)	PCR Self: 82.5 Clin: 87.5 HC2 Self: 80.0 Clin: 90.0	PCR Self: 93.6 Clin: 93.2 HC2 Self: 88.1 Clin: 91.7	PCR Self: 52.4 Clin: 52.2 HC2 Self: 38.4 Clin: 48.0	PCR Self: 98.4 Clin: 98.9 HC2 Self: 98.1 Clin: 99.1
Fwu et al. (2011)(55) §	252 women evaluated for abnormal cytology or abnormal colposcopy (colposcopy clinic)	Colposcopy (all women)	MY11/MY09 nested GP5+/6+-PCR	Vaginal vs cervical brush	Self: 75.0 Clin: 87.5 P=0.48	Self: 75.8* Clin: 73.7*	Self: 17.4* Clin: 18.4*	Self: 97.8* Clin: 98.9*
Dijkstra et al. (2012)(39)	135 symptomatic women (gynaecologic clinic)	Colposcopy (all women)	HR GP5+/6+-PCR	Vaginal vs cervical brush	Self: 93.0 Clin: 90.7	Self: 51.1 Clin: 51.2	Self: 47.1* Clin: 46.4*	Self: 94.0* Clin: 92.2*

Sensibilità: minore o uguale

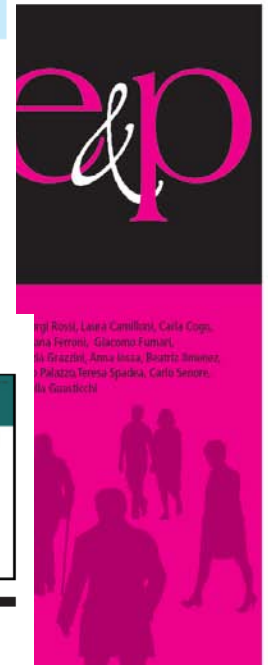
Specificità: minore o non rilevante

Obiettivo

- Valutare l'efficacia del self sampling nell'aumentare la partecipazione nelle donne non rispondenti allo screening.

Metodi

- Revisione sistematica aggiornata al 31/07/2012
- Parte di una revisione più ampia sui metodi per aumentare la partecipazione agli screening
- MEDLINE, EMBASE, Cochrane, PsycINFO, LILACS, HTA, and CRD.
- Letteratura grigia italiana dai siti delle regioni, ministero, ONS. Altri siti ministeri paesi UE, IARC, WHO.
- Crosscheck delle referenze.



ngi Rossi, Luisa Camilloni, Carla Cognigni, Eliana Ferroni, Giacomo Furnari, Beatriz Jimenez Cendales, Annamaria Pezzarossi, Piero Borgia, Gabriella Guasticchi, Paolo Giorgi Rossi, Carlo Scovazzi, Carlo Guasticchi

Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test

Preventive Medicine 55 (2012) 587–596

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Review

How to increase uptake in comparing population-based

BMC Public Health



E. Ferroni^a, L. Camilloni^a, B. Jimenez and the Methods to increase parti

This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

Methods to increase participation in organised screening programs: a systematic review

BMC Public Health 2013, **13**:464 doi:10.1186/1471-2458-13-464

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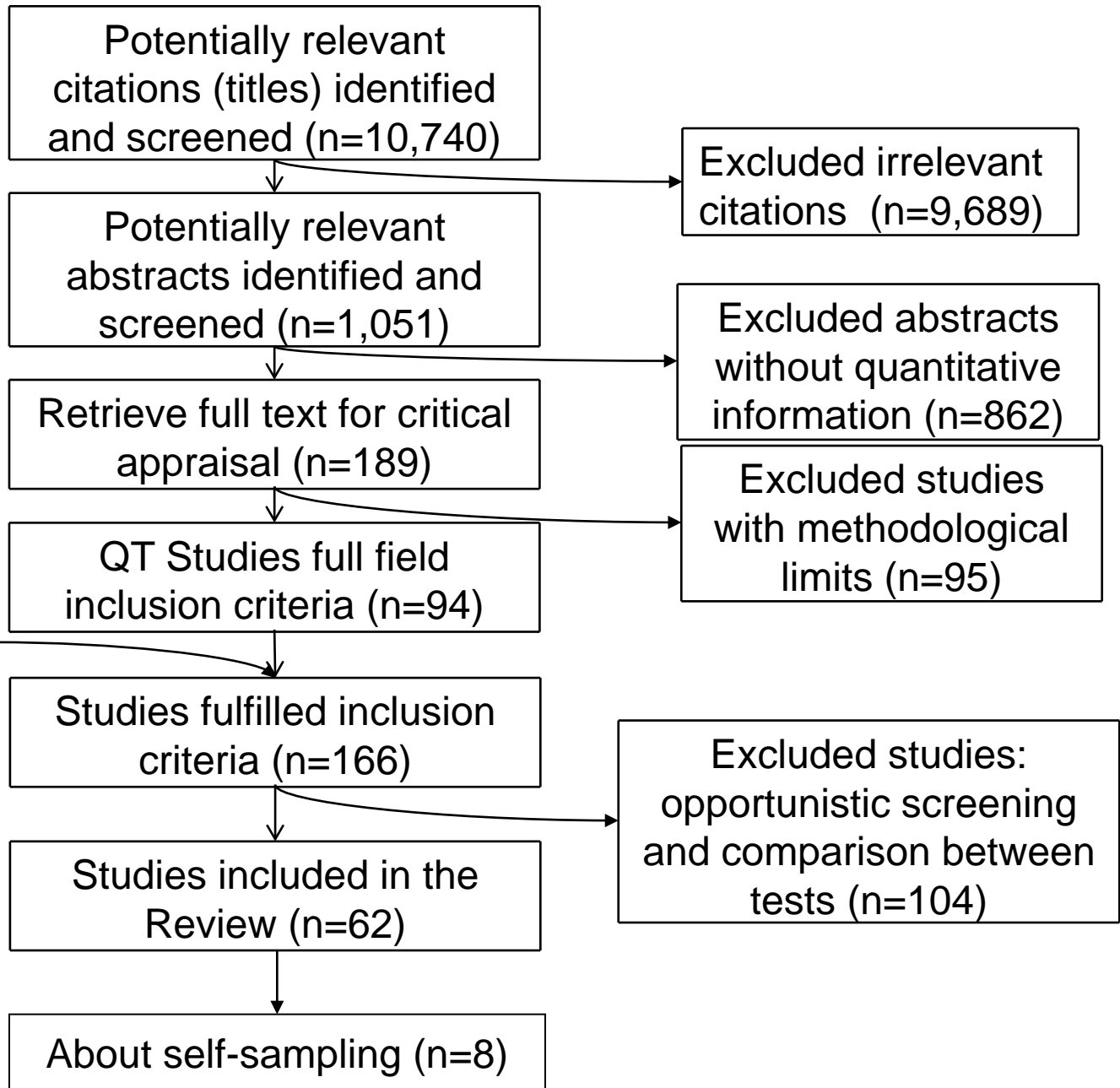
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Flow chart studi inclusi ed esclusi



Risultati studi identificati

AUTHOR	YEAR	SETTING	STUDY	POPULATION	OUTCOMES OF INTEREST	n/N Intervention	n/N Control
Giorgi Rossi	2011	Italy	RCT	35-65	Main: women's participation in screening. Secondary: the impact on screening coverage	I1 622/2480; I2 616/2480	C1 619/2480; C2 617/2480
Gok	2010	Netherlands	RCT	>33	Participation rate in both groups and yield of cervical intraepithelial neoplasia grade II/III or worse in self sampling responders	26886/27163	277/27163
Gok	2012	Netherlands	RCT	women who turned in their 30th, 35th, 40th, 45th, 50th, 55th or 60th birth year	Participation rate	26145/26409	264/26409
Lazcano-Ponce	2011	Mexico	RCT	25-65	CIN 2 or worse, detected by colposcopy	12330/25061	12731/25061
Piana	2011	France	RCT	35-69	Participation rate	4400/9334	4934/9334
Szarewski	2011	UK	RCT	no specification (screening age)	Participation rate	1500/3000	1500/3000
Virtanen	2011	Finland	RCT	30-60	Participation rate	7027/25404	18377/25404
Wikström	2011	Sweden	RCT	39-60	Participation rate	2000/4060	2060/4060

Risultati risk of bias

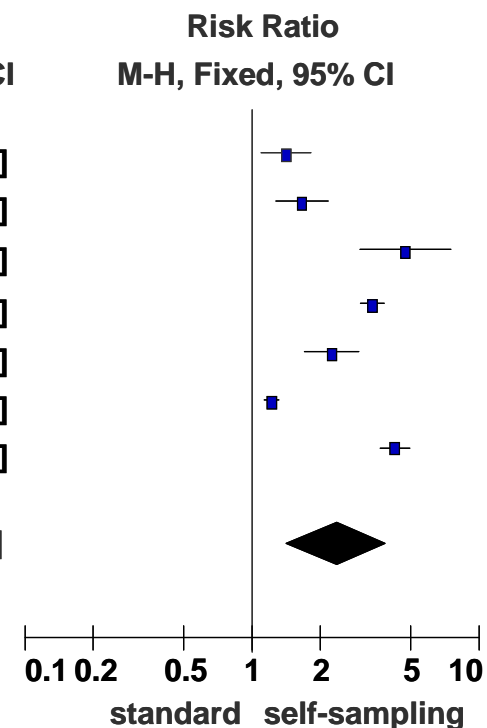
Paper	Year	Sequence generation	Concealment	Blinding of assessor	Incomplete outcome data	Selective outcome reporting	Pre-selected population	ITT
Giorgi Rossi	2011	😊	😞	😞	100% I1; 99% I2; 100% C1; 100% C2	😊	😊	😊
Gok	2010	😊	😞	😞	97% I; 99% C	😊	😊	😊
Gok	2012	😊	😞	😞	98% I; 99% C	😊	😊	😊
Lazcano-Ponce	2011	😊	😞	😞	76% I; 100% C	😊	😊	😞
Piana	2011	😊	😞	😞	81% I; 87% C	😊	😊	😞
Szarewski	2011	😊	😞	😞	100% I; 100% C	😊	😊	😊
Virtanen	2011	😊	😊	😞	100% I; 100% C	😊	😊	😊
Wikström	2011	😊	😊	😞	100% I; 100% C	😊	😊	😊

Risultati forrest plot

Study and country	self-sampling direct mail		standard recall		Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total	
Giorgi Rossi 2011 Italy	121	616	86	619	1.41 [1.10, 1.82]
Gok 2010 Netherlands	7404	26920	46	277	1.66 [1.27, 2.16]
Gok 2012 Netherlands	7870	25561	17	261	4.73 [2.98, 7.49]
Piana 2011 France	939	4400	311	4934	3.39 [3.00, 3.82]
Szarewski 2011 UK	153	1500	68	1500	2.25 [1.71, 2.97]
Virtanen 2011 Finland	756	2397	1631	6302	1.22 [1.13, 1.31]
Wikström 2011 Sweden	779	2000	188	2060	4.27 [3.68, 4.94]
Total (95% CI)		63394		15953	2.37 [1.44, 3.90]
Total events	18022		2347		

Heterogeneity: $\text{Tau}^2 = 0.44$; $\text{Chi}^2 = 389.85$, $\text{df} = 6$ ($P < 0.00001$); $I^2 = 98\%$

Test for overall effect: $Z = 3.38$
($P = 0.0007$)

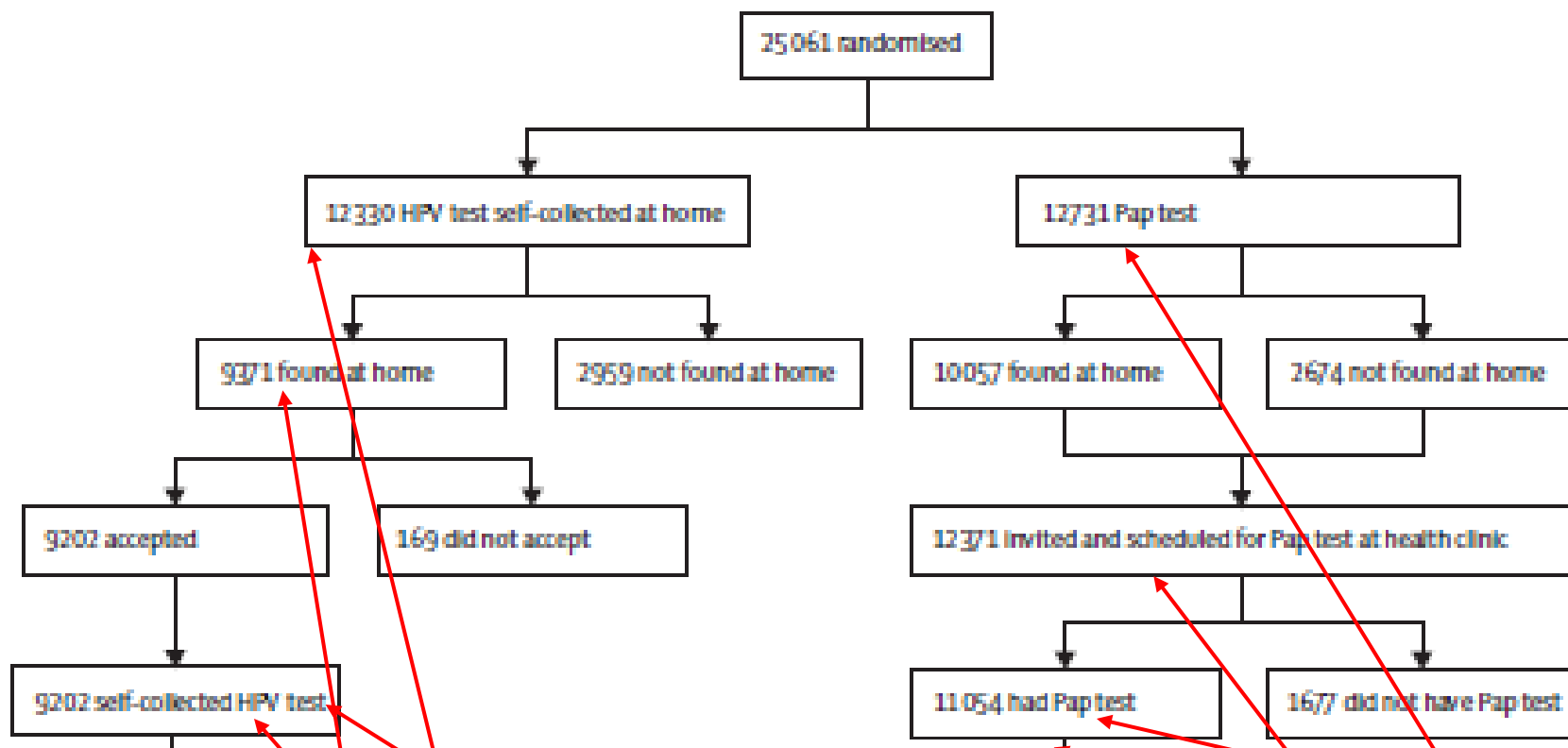


Risultati: studi non pubblicati

Nuovo studio francese (in press Piana, et al Int J Cancer):

- Programma “organizzato” a bassa adesione in popolazione deprivata
- Risultati paragonabili al primo studio
- Bassa compliance al follow up.

Risultati lazcano ponce



HPV su randomizzati: 74.6%

HPV su spediti: 98.2%

Pap su randomizzati: 89.7%

Pap su contattati: 89.4%

Risultati Lazcano-Ponce: detection rate

Nonostante abbia screenato
il 74% vs 89%
Trovo 37 vs 13 CIN3+

	HPV (CIN 2 or worse)	Pap (CIN 2 or worse)	HPV (CIN 3 or worse)	Pap (CIN 3 or worse)
25-65 years				
N	884	42	884	42
CIN 2 or worse	108	38	48	18
PPV (95% CI)	12.2 (9.9-14.5)	90.5 (61.7-100.0)	5.4 (3.9-7.0)	42.9 (23-62.7)
30-65 years				
N	682	32	682	32
CIN 2 or worse	99	30	45	16
PPV (95% CI)	14.5 (11.7-17.4)	93.7 (60.2-100.0)	6.6 (4.7-8.5)	50.0 (25.5-74.5)
35-65 years				
N	511	25	511	25
≥CIN 2 or worse	85	23	37	13
PPV (95% CI)	16.6 (13.1-20.2)	92.0 (54.4-100.0)	7.2 (4.9-9.6)	52.0 (23.7-80.3)
HPV=human papillomavirus. CIN=cervical intraepithelial neoplasia. PPV=positive predictive value.				
Table 3: Positive predictive value of the HPV test and Pap cytology test by age				



Risultati: impatto sulla copertura di popolazione

- Italia: Di 90 donne che hanno risposto all'invio diretto del self sampler 4 non avevano mai fatto il Pap e 30 lo avevano fatto più di 3aa prima (14 oltre 5aa).
- L'aumento di copertura nella popolazione generale stimato è del 4% (95%CI 2.7-4.7).
- Il numero di dispositivi da spedire per ottenere un campione è 5, per donna coperta è 15.

Risultati: costo efficacia

Costo totale self sampling: spedizione 1.5×2 valori bollati + 0.35 di buste + 13 dispositivo = 16.35€

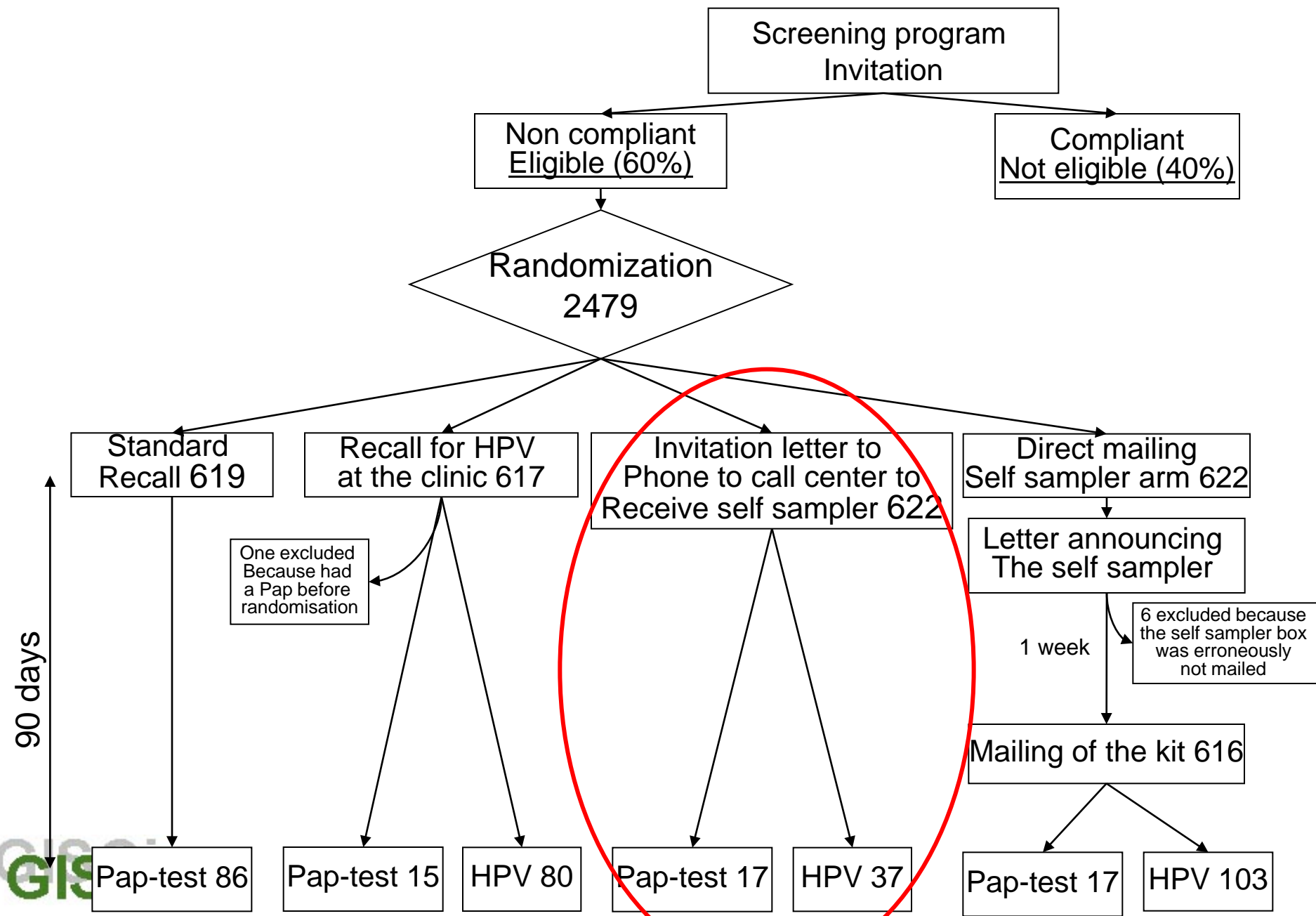
Costo sollecito: lettera 0.95 + quello per il prelievo citologico 7.2 = 8.15€

A Roma il costo per donna conquistata dallo screening è: $((3.35+13) \times (.923)) - (7.2 \times 0.1) / 0.09 = 160€$

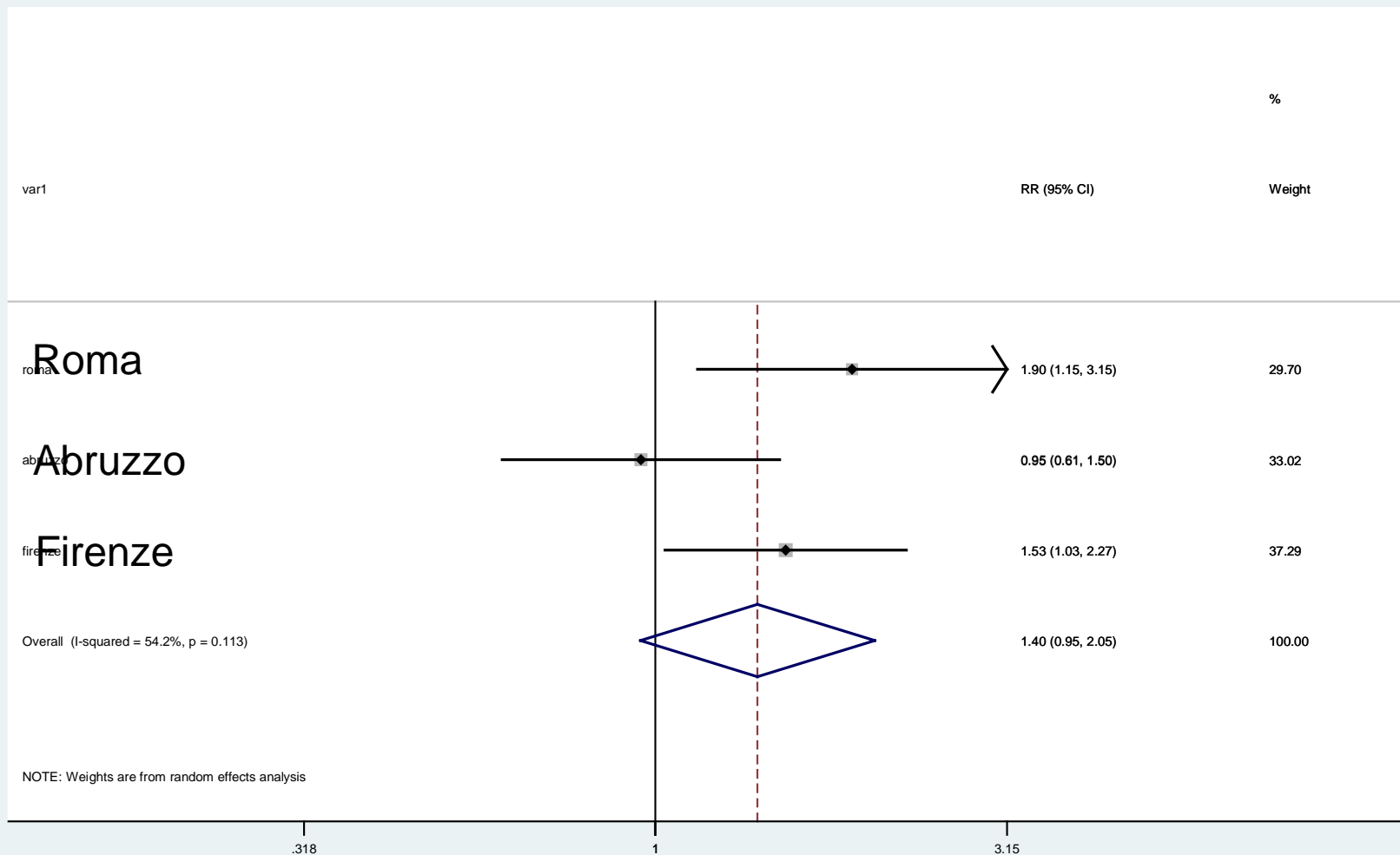
A Firenze : $((3.35+13) \times (.93)) - (7.2 \times 0.143) / 0.075 = 189€$

In Abruzzo non c'è efficacia.

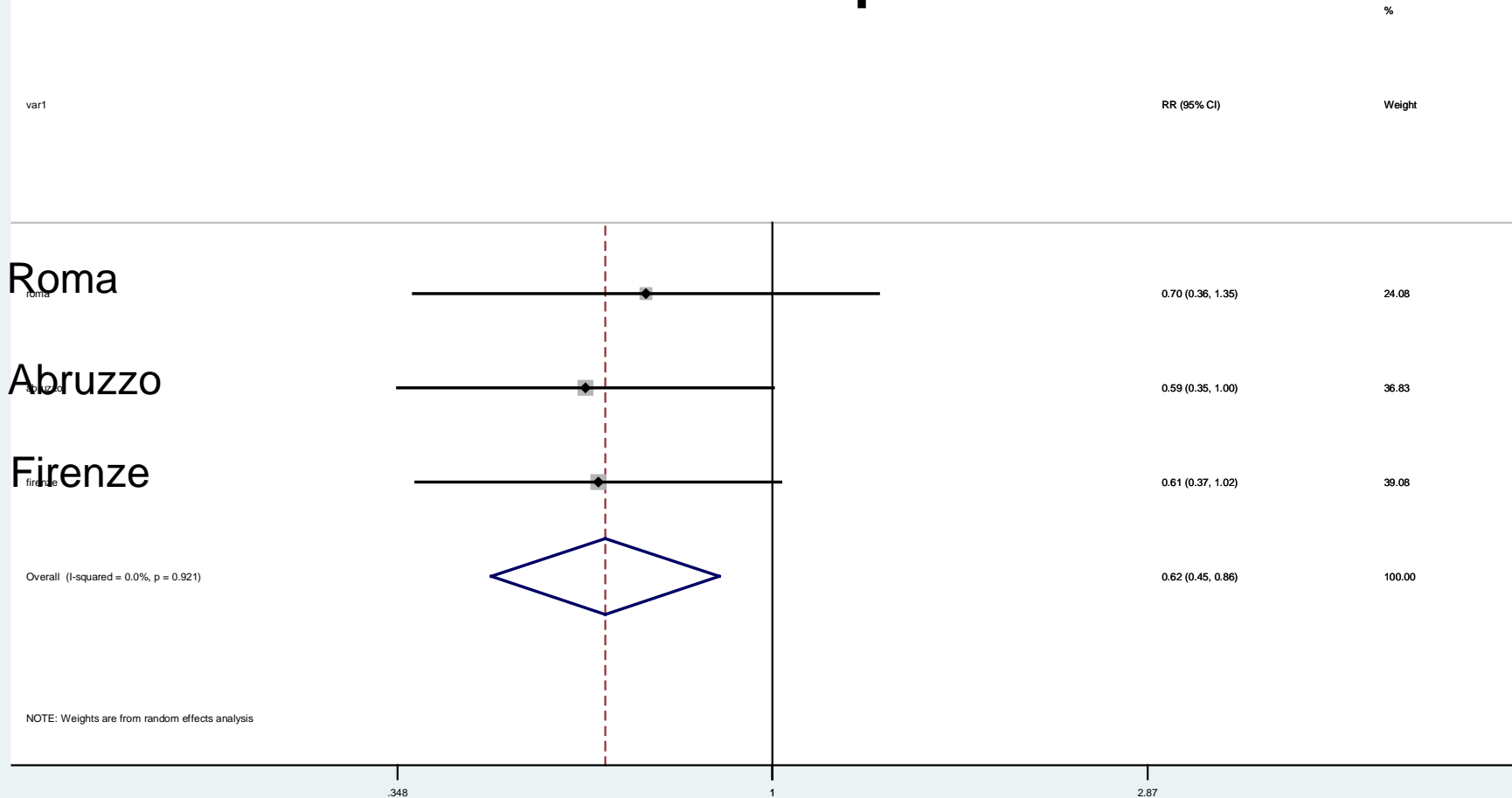
Bisogna ridurre il numero di dispositivi persi!



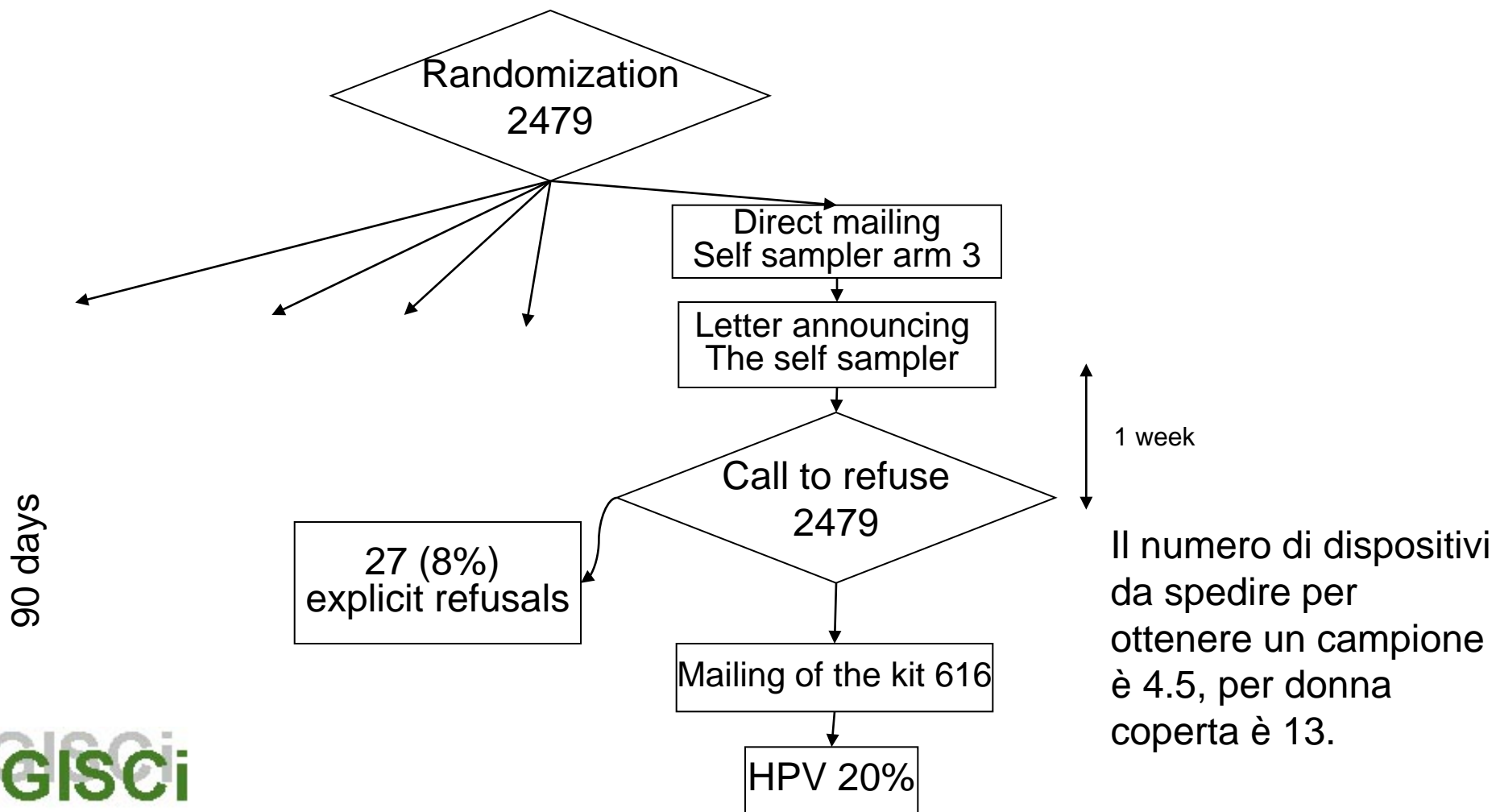
Risultati trial italiano: invio a casa



Risultati trial italiano: invito a ritirare il self-sampler



Il vecchio trial italiano: il 5 braccio



Prospettive

- Uso per primo invito? (studio Messicano)
- Ridurre costi prelievo?
- Solo campagne in mai screenate?
- Follow up molecolare su stesso prelievo:
- Tipizzazione, già fattibile (uno studio francese, scarsi risultati)
- mRNA E6/E7 (ancora da sviluppare)

Conclusioni

- Il self sampling aumenta l'adesione nelle non rispondenti (tranne in Abruzzo)
- Il braccio "on demand" non ha funzionato.
- Il ritiro in farmacia non ha funzionato (tranne a Roma G)
- Ogni tentativo di ridurre i dispositivi persi è fallito.
- L'uso come primo approccio ha funzionato in Messico

Dilemma

Self sampling come primo approccio:

- È accettabile usare un test meno specifico e meno sensibile rispetto a HPV, ma \geq citologia.
- Forte riduzione dei costi per prelievo
- Aumento compliance da verificare...

Grazie per l'attenzione
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GISCI

*Gruppo Italiano Screening del Cervicocarcinoma
Venezia, 27-28 Maggio 2010*