



Cervical Cancer Consortium Europe

2nd European Conference on Cervical Cancer Screening

Tübingen (Germany), September 19-20, 2005

***Meta-analysis of the diagnostic properties of
HPV testing in the triage of borderline and low
grade cytological lesions***

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Clinical Applications of HPV testing

- 1. Triage of women with equivocal/low-grade lesions (*)**
- 2. Follow-up of women with CIN2/3 treated with local surgery: prediction of residual/recurrent CIN**
- 3. Primary cervical cancer screening**



Triage of minor cytological lesions with HPV

- **Systematic review and meta-analysis**
- **Publications:**
 - **IPH / EPI – REPORTS Nr. 2001- 019**
 - **ASCUS triage: JNCI 2004a & b**
 - **ASCUS & LSIL triage: Gynecol Oncol 2005**
 - **Registered by the Cochrane Gynecological Cancer Collaborative Review Group**



Triage of women with minor cytological lesions

Inclusion criteria for retrieved references

- **Women with previous smear showing ASCUS or LSIL**
- **Application of HPV DNA test**
- **Optionally: repeat cytology**
- **All cases submitted to golden standard verification: colpo/biopsy/EC**
- **Published**



30 references included

1. Bavin PJ et al, 1993: Cancer (LSIL)
2. Goff BA et al, 1993: Gynecol Oncol (ASCUS)
3. Slawson DC et al, 1994: J Fam Pract (ASCUS)
4. Cox JT et al, 1995: Am J Obstet Gynecol (ASCUS)
5. Herrington CS et al, 1995: Br J Cancer (ASCUS/LSIL)
6. Hall S et al, 1996: Gynecol Oncol (ASCUS/LSIL)
7. Wright TC et al, 1995: Obstet & Gynecol (ASCUS & LSIL)
8. Chesebro MJ et al, 1997: J Lower Genit Tract Dis (LSIL)
9. Kaufman RH et al, 1997a: Am J Obs Gynecol (ASCUS/LSIL)
10. Kaufman RH et al, 1997b: Am J Obst Gynecol (ASCUS/LSIL)
11. Adam E et al, 1998: Am J Obstet Gynecol (ASCUS/LSIL)
12. Fait G et al, 1998: Gynecol Oncol (ASCUS & LSIL)
13. Ferris DG et al, 1998 (a): J Fam Pract (ASCUS & LSIL)
14. Ferris DG et al, 1998 (b): J Fam Pract (ASCUS & LSIL)
15. Nyirjesy I et al, 1998: Obstet Gynecol (ASCUS/LSIL)
16. Sideri M, 1998: Cancer Epid, Biom & Prev (LSIL)
17. Wright et al, 1998: Am J Obstet Gynecol (ASCUS/LSIL)
18. Manos MM et al, 1999: JAMA (ASCUS)
19. ALTS group, 2000: JNCI (LSIL)
20. Bergeron C et al, 2000: Obstet Gynecol (ASCUS & LSIL)
21. Fait G et al, 2000: Gynecol Oncol (ASCUS & LSIL)
22. Lin CT et al, 2000: J Reprod Med (ASCUS & LSIL)
23. **Lytwyn A et al, 2000: CMAJ (ASCUS & LSIL)**
24. Mould TAJ et al, 2000: Eur J Gynaecol Oncol (ASCUS&LSIL)
25. Shlay JC et al, 2000: Obstet Gynecol (ASCUS)
26. Morin C et al, 2000: J Reprod Med (ASCUS)
27. Rebello G et al, 2001: BMJ (ASCUS & LSIL, ASCUS/LSIL)
28. **Solomon D et al, 2001: JNCI (ASCUS)**
29. Zielinski GD al, 2001: J Pathol(ASCUS; LSIL;ASCUS/LLSIL)
30. **Sherman ME et al, 2002: JNCI (ASCUS & LSIL)**



13 additional references included

1. Kuperman L et al, 2000: J Low Genit Tract Dis (ASCUS)
2. Hughes SL et al, 2002: Am J Obstet Gynecol (ASCUS)
3. Kulasingam SL et al, 2002: JAMA (ASCUS & LSIL)
4. Pambucian SE et al, 2002: Am Soc Cytopathol (ASCUS)
5. Pretorius RG et al, 2002: J Reprod Med (ASCUS & LSIL)
6. Guyot A et al, 2003: BMC Infect Dis (ASCUS & LSIL)
7. Ho L et al, 2003: J Med Virol (ASCUS/LSIL)
8. Lonky NM et al, 2003: Obstet Gynecol (ASCUS & LSIL)
9. Pisal N et al, 2003: Acta Obstet Gynecol Scand (ASCUS/LSIL)
10. Qureshi MN et al, 2003: Diagn Cytopathol (ASCUS/LSIL)
11. Santos C et al, 2003 : Sao Paulo Med J (ASCUS/LSIL)
12. Wensveen C et al, 2003: Acta Obstet Gyn Scand (ASCUS & LSIL)
13. Dalla Palma P et al, 2005: Cytopathol (ASCUS)



Experimental methods

- **Randomised trials: repeat cytology vs. HPV test (Lytwyn, 2000; ALTS, 2001)**
- **Concomitant testing: all tests on the same women**



Outcomes

- **CIN2+**
- **CIN3+**

Triage test thresholds

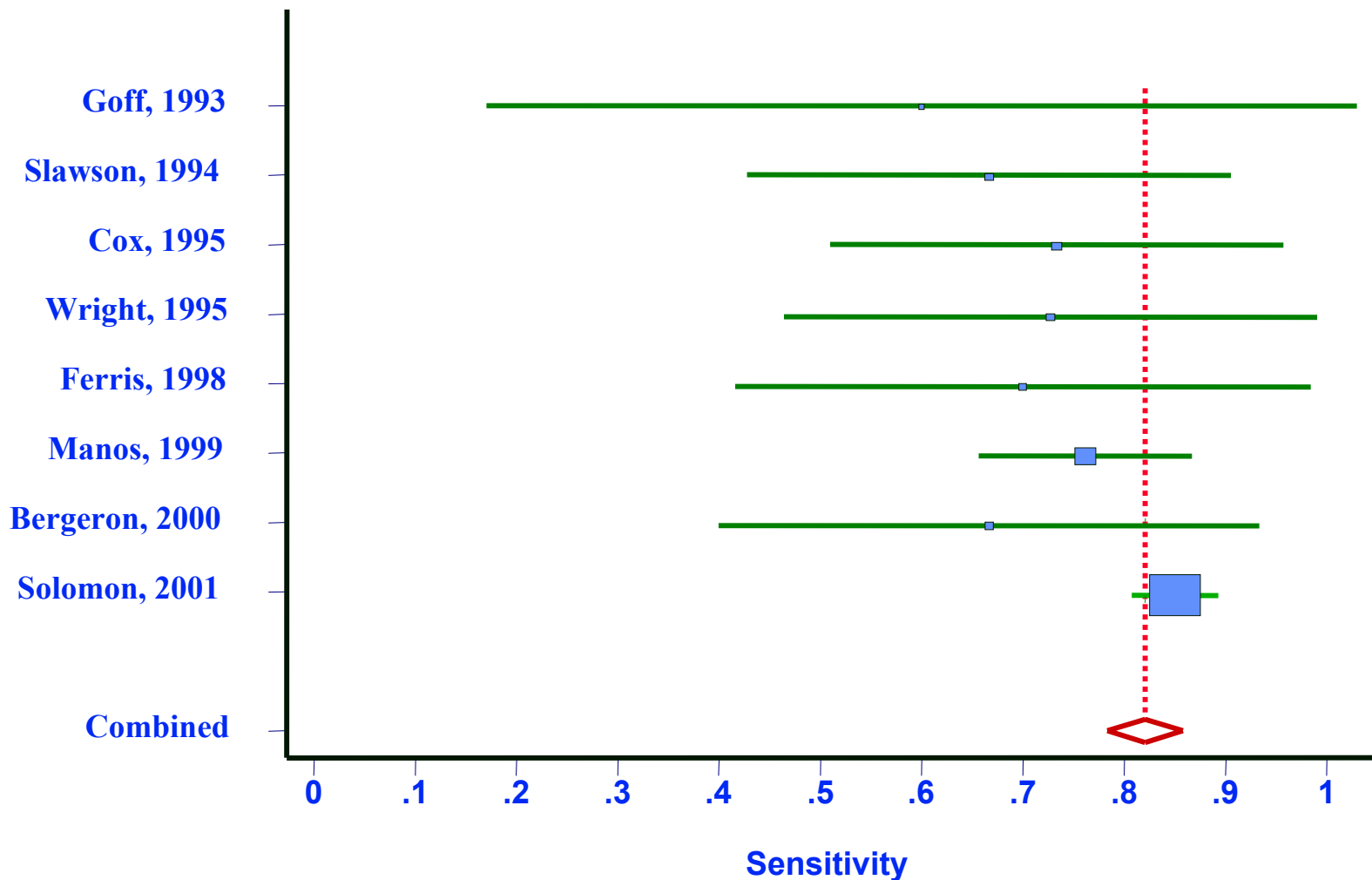
- **For cytology: ASCUS+, LSIL+, HSIL+**
- **For HPV testing:**
 - **Detectable presence of target DNA**
 - **HC: determined in luminescence unit (RLU>1)**



Triage of women with index smear=ASCUS

Meta-analysis of sensitivity of repeat cytology

Outcome: CIN 2+, threshold for repeat cytology: \geq ASCUS

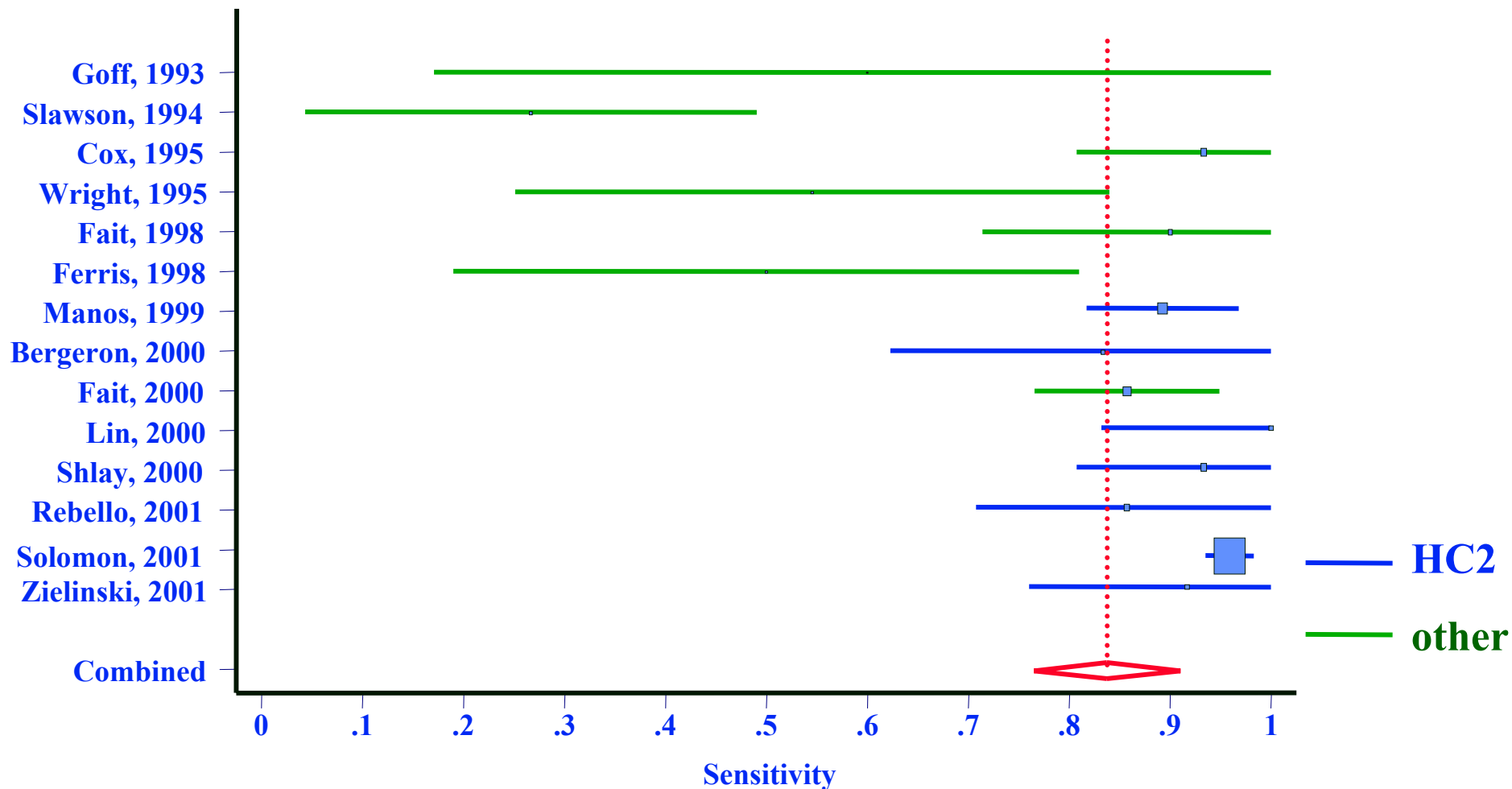




Triage of women with index smear=ASCUS

Meta-analysis of sensitivity of HPV DNA detection

Outcome: CIN 2+, HPV DNA test = positive

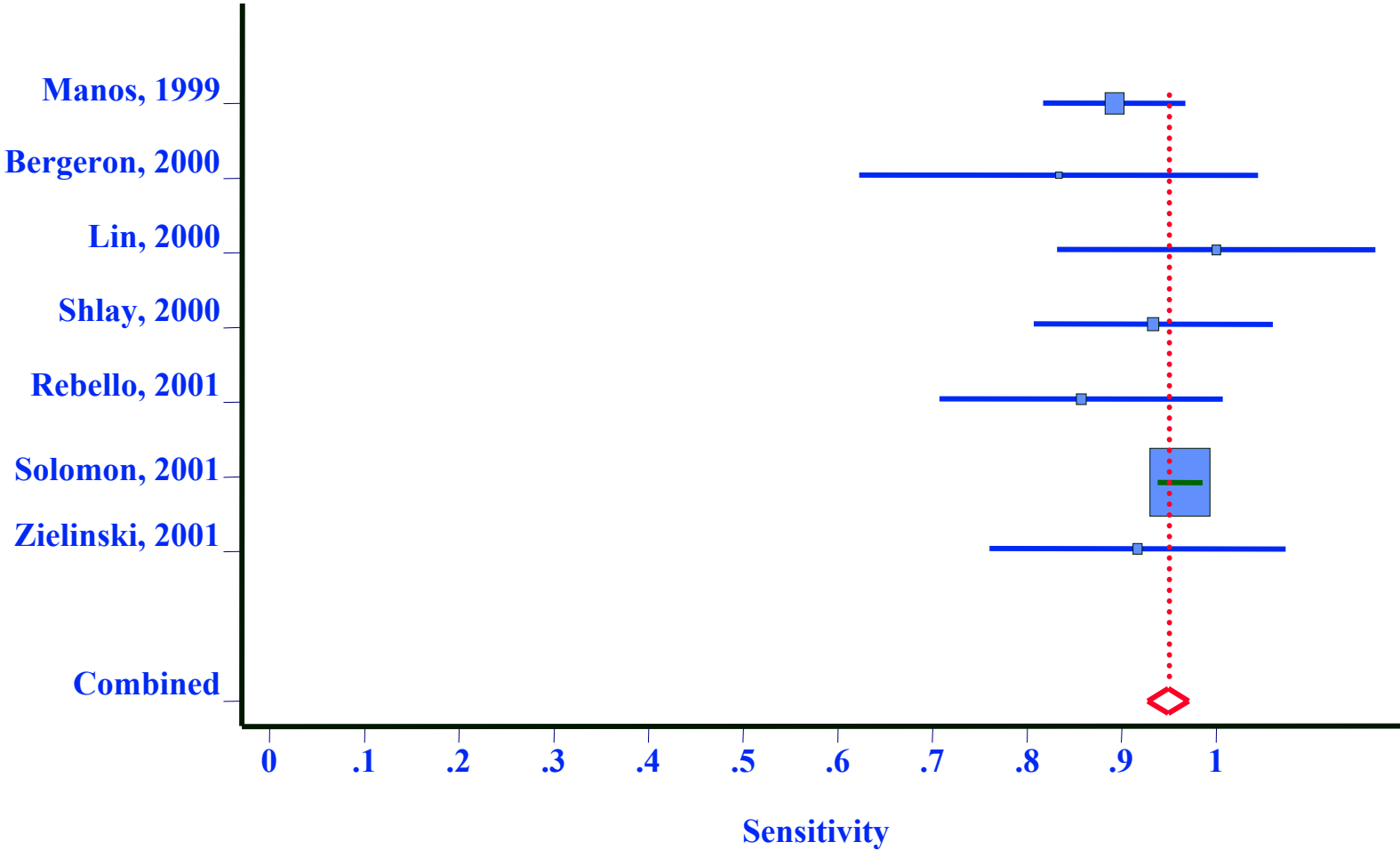




Triage of women with index smear=ASCUS

Meta-analysis of sensitivity of Hybrid Capture 2 test

Outcome: CIN 2+, RLU>=1





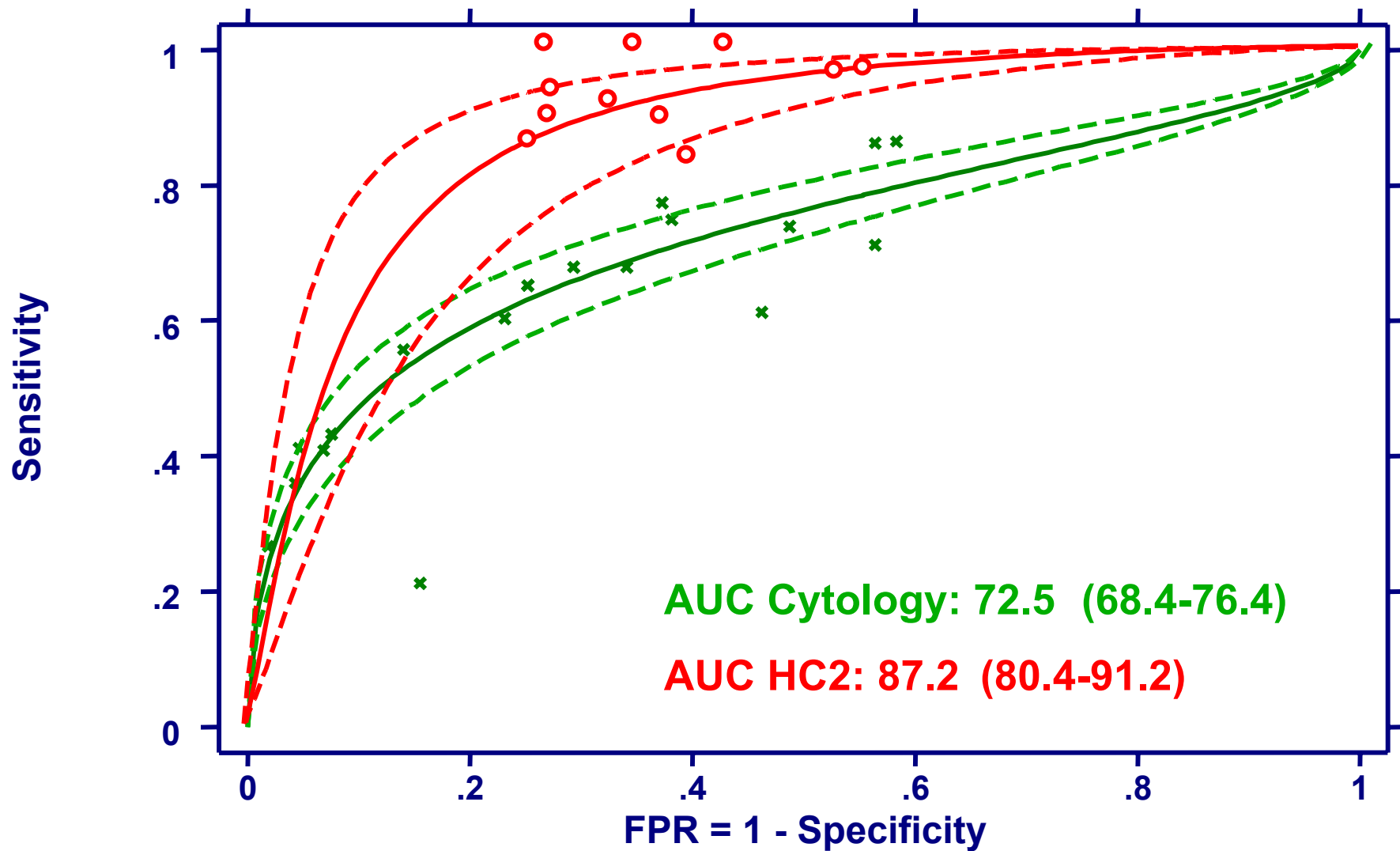
Triage of ASCUS cases

Outcome=CIN2+, pooled estimates & CI

Test threshold	Cytology >=ASCUS 11 studies	HC2 RLU>=1 16 studies
Sensitivity	81.4 (77.9-85.0)	<u>94.0</u> (92.1-95.9)
Specificity	58.8 (51.3-66.2)	62.4 (56.3- 68.4))
PPV	12.8 (9.0-16.7)	<u>22.3</u> (18.2-26.4)
NPV	96.7 (96.0-97.4)	<u>98.9</u> (98.5-99.2)
Test+	43.9 (36.3-51.5)	44.7 (38.4-12.5)
Prevalence		10.3 (8.2-12.5)

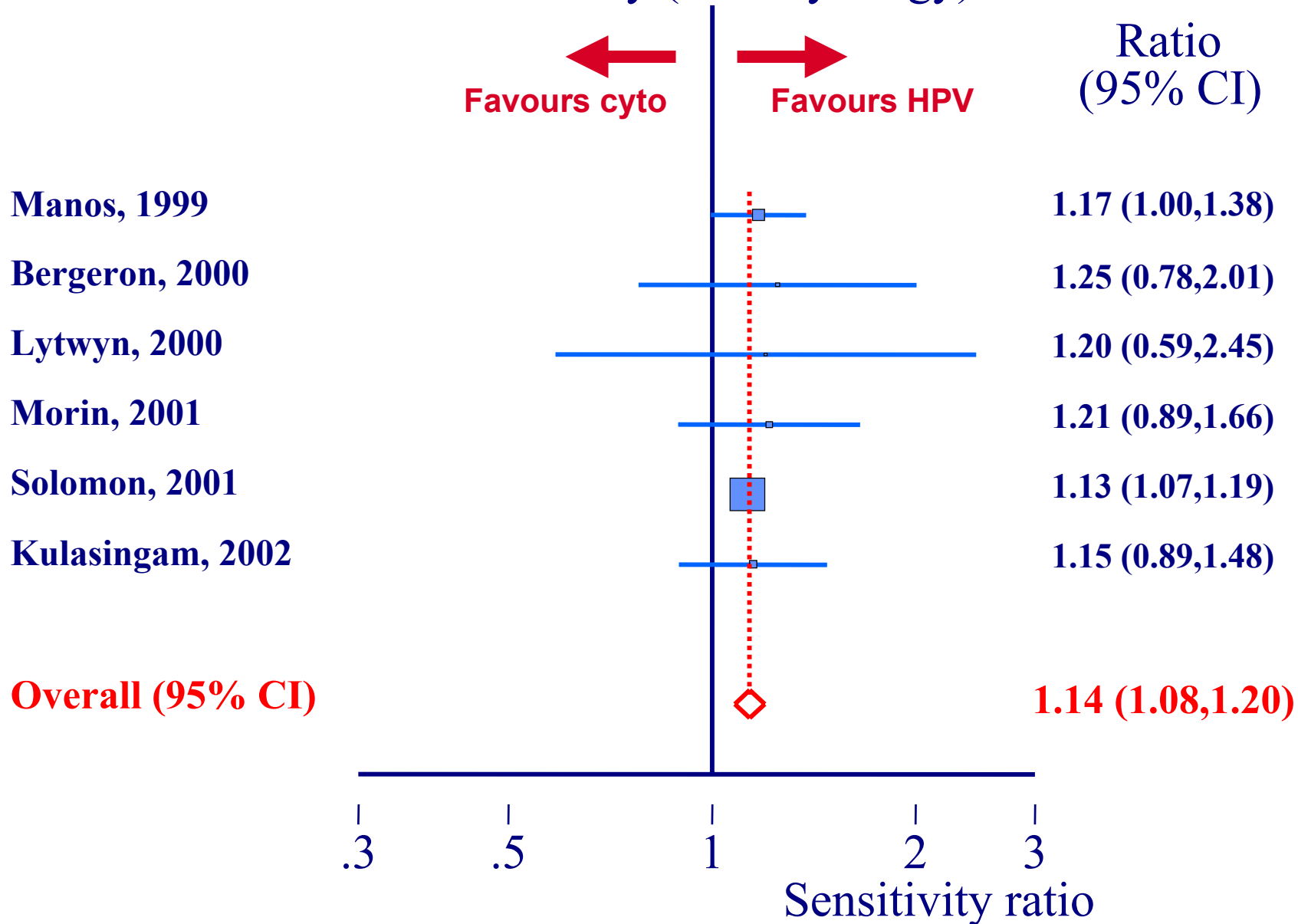


Area under the SROC curve



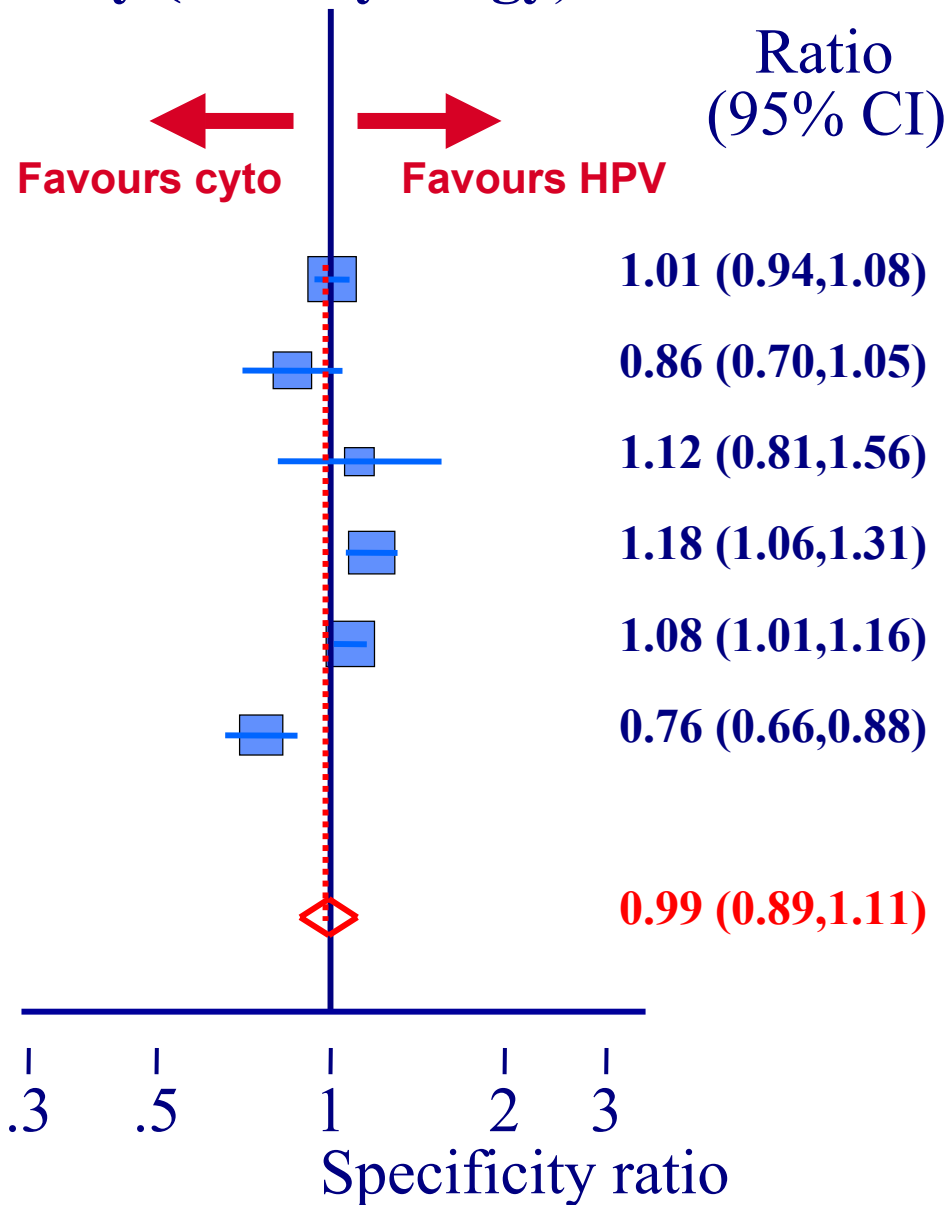
Triage of ASCUS

ratio of sensitivity (HC2/cytology)





Triage of ASCUS ratio of specificity (HC2/cytology)





J Natl Cancer Inst 2004; 96: 1401-2

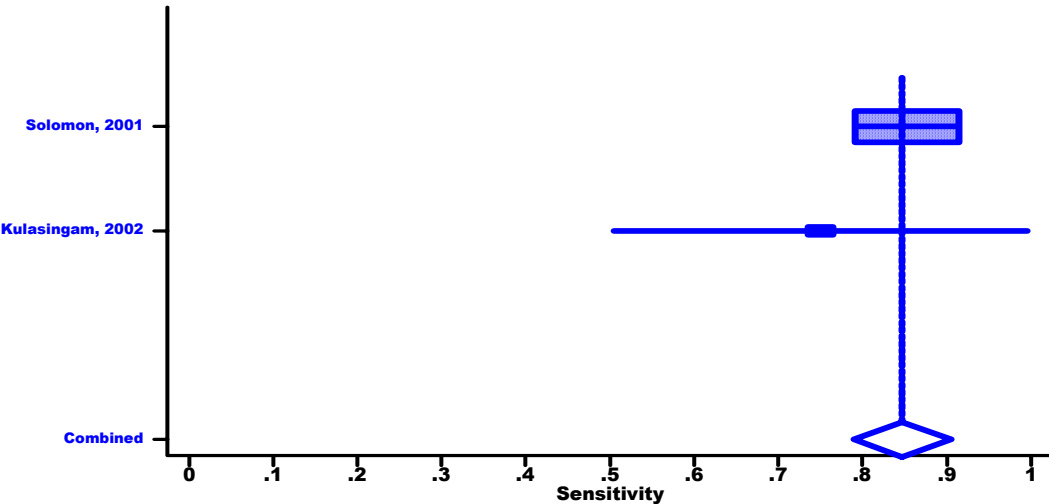
Meta-analysis: CIN3+ outcome

Study	N	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence CIN3+
<i>Triage test: Hybrid Capture-2</i>				
Lin, 2000 (5)	74	1.000 (0.768 to 1.000)	0.583 (0.449 to 0.709)	0.189
Solomon, 2001 (3)	2310	0.963 (0.916 to 0.988)	0.458 (0.437 to 0.479)	0.059
Zielinski, 2001 (6)	213	1.000 (0.398 to 0.665)	0.665 (0.597 to 0.729)	0.019
Lonky, 2003 (7)	213	0.933 (0.681 to 0.998)	0.697 (0.628 to 0.760)	0.070
Pooled	2810	0.964^f (0.935 to 0.999)	0.565^r (0.455 to 0.675)	0.057
<i>Triage test: repeat cytology</i>				
Solomon, 2001 (ASCUS+) (3)	2317	0.853 (0.784 to 0.903)	0.427 (0.407 to 0.448)	0.059
Solomon, 2001 (LSIL+) (3)	2317	0.640 (0.557 to 0.716)	0.759 (0.740 to 0.776)	0.059
Solomon, 2001 (HSIL+) (3)	2317	0.441 (0.360 to 0.525)	0.954 (0.945 to 0.962)	0.059

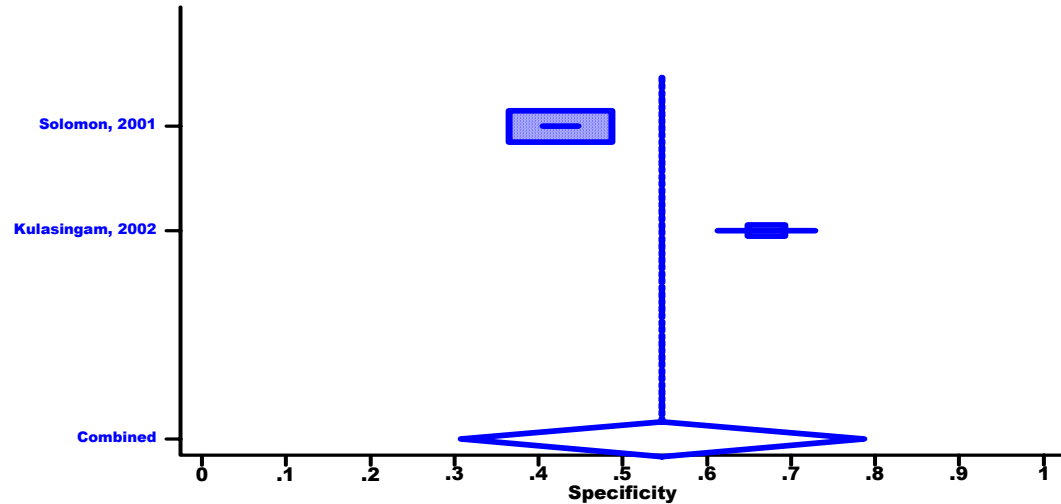


Meta-analysis: CIN3+ outcome

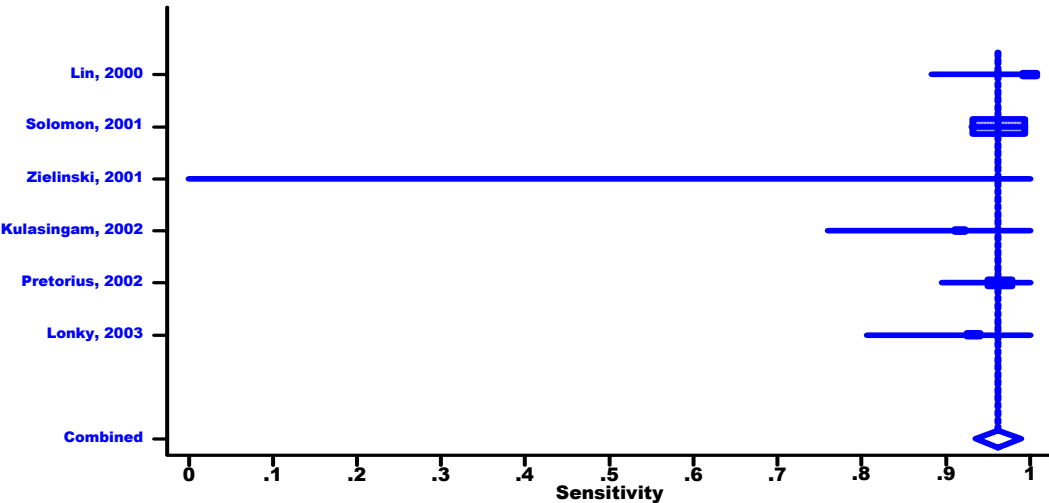
Triage of ASCUS. Outcome: CIN 3+
Cytology cut-off \geq ASCUS



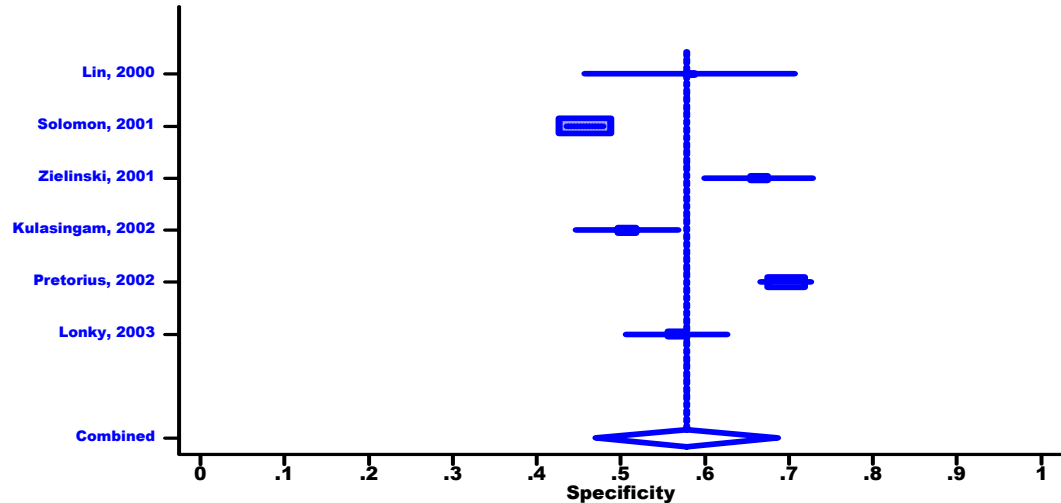
Triage of ASCUS. Outcome: CIN 3+
Cytology cut-off \geq ASCUS



Triage of ASCUS. Outcome: CIN 3+
HC2, RLU >1



Triage of ASCUS. Outcome: CIN 3+
HC2, RLU >1



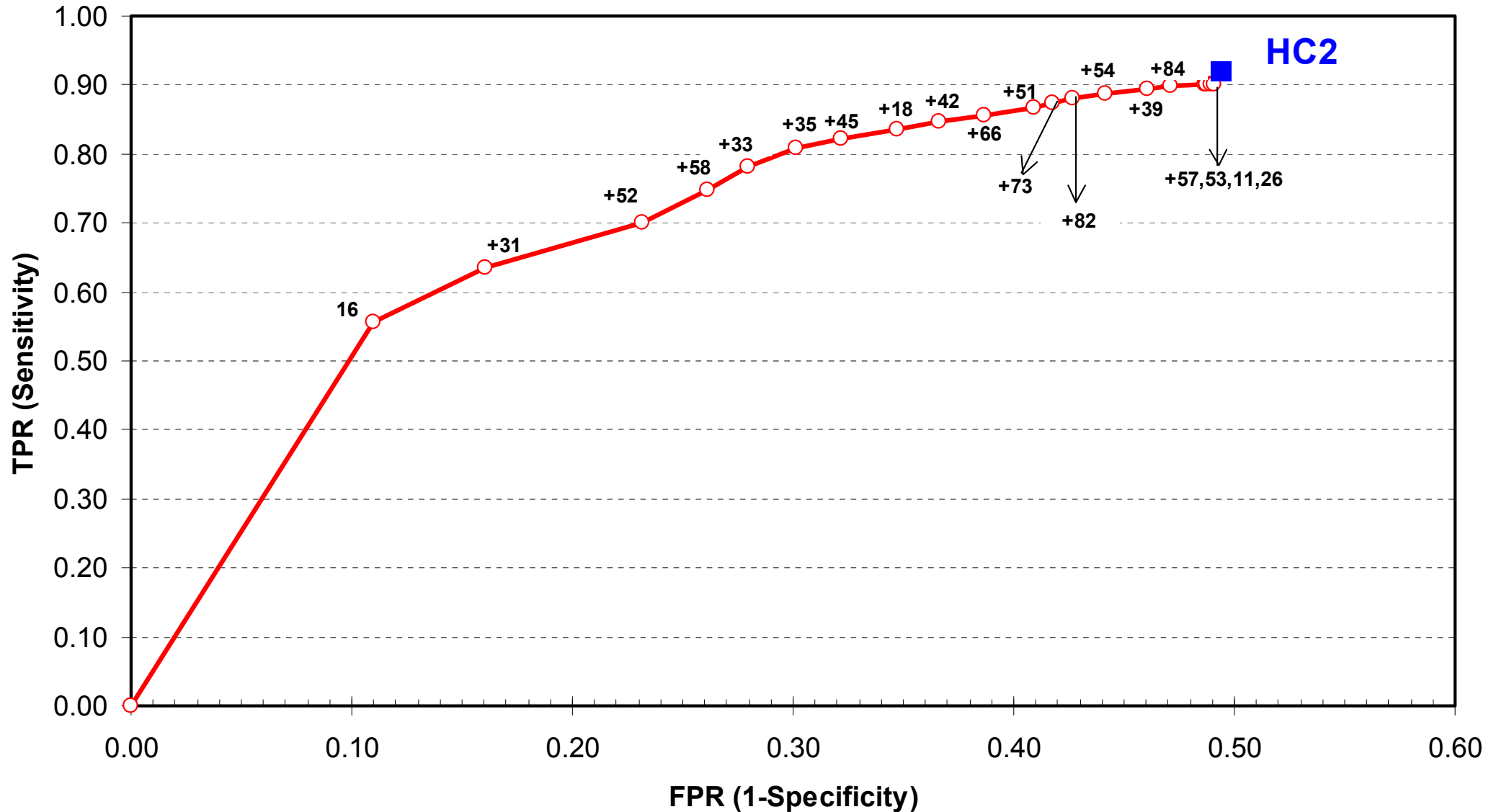


Influence of age on accuracy of triage of ASCUS (outcome CIN2+)

Study	Test	Age group (years)	Sensitivity (95% CI)	Specificity (95% CI)
Shlay, 2001	HC2 (>1pg/mL)	<30	1.00 (0.63-1.00)	0.57 (0.45-0.69)
		30+	0.86 (0.42-1.00)	0.84 (0.76-0.90)
Sherman, 2002*	Cytology (ASCUS+)	18-22	0.82 (0.92-0.99)	0.37 (0.33-0.41)
		23-28	0.90 (0.83-0.95)	0.41 (0.37-0.45)
		29+	0.85 (0.73-0.94)	0.52 (0.50-0.56)
	HC2 (>1pg/mL)	18-22	0.97 (0.92-0.99)	0.34 (0.30-0.37)
		23-28	0.94 (0.88-0.99)	0.40 (0.36-0.44)
		29+	0.96 (0.86-1.00)	0.73 (0.70-0.76)

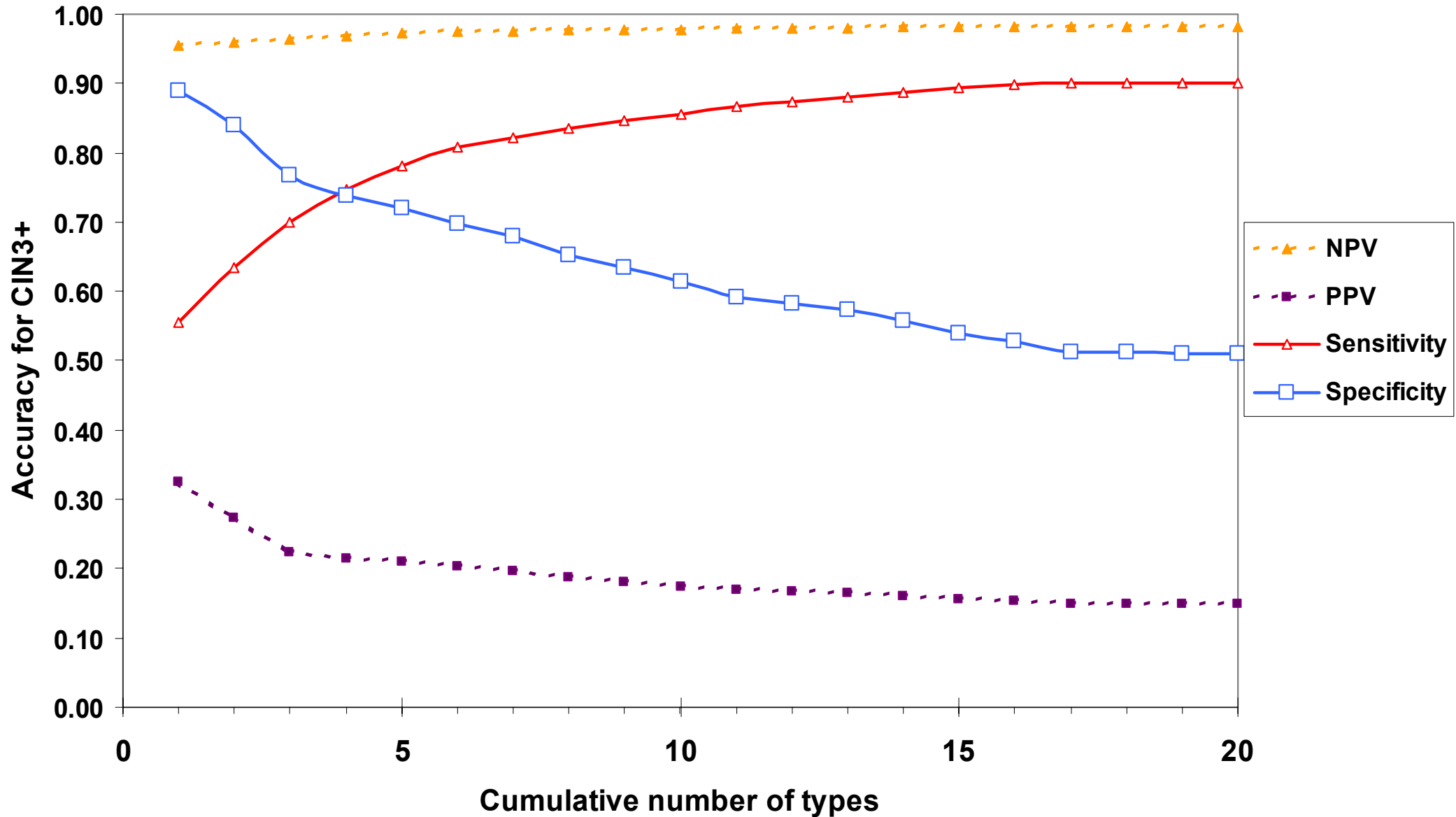
ALTS, Schiffman, JNCI 2005

Triage of ASCUS, using multiple HPV geno-typing (outcome CIN3+)



ALTS, Schiffman, JNCI 2005

Triage of ASCUS, using a cumulative number of HPV types



Triage of ASCUS, using a HPV RNA testing

(Pretect HPV Proofer: HPV 16,18,31,33,45)

Test	Outcome	TP	FN	FP	TN
HPV Proofer	CIN2+	2	0	9	43
GP5+/6+		2	0	23	29

	Sensitivity	Specificity	Test + rate	PPV	NPV
Proofer	100.0%	82.7%	20.4%	18.2%	100.0%
GP5+/6+	100.0%	55.8%	46.3%	8.0%	100.0%

95% CI around specificity

Proofer (70.7-91.8%)

GP5+/6+ (41.3-69.5%)

Molden, Int J Cancer 2005



Conclusions: triage of ASCUS

- **Evidence is available indicating improved cross-sectional accuracy of the HC II assay in comparison with repeat cytology for detection of CIN2+**
- **Obsolete HPV DNA detection systems less accurate**
- **Insufficient data on PCRs**



Triage of LSIL cases

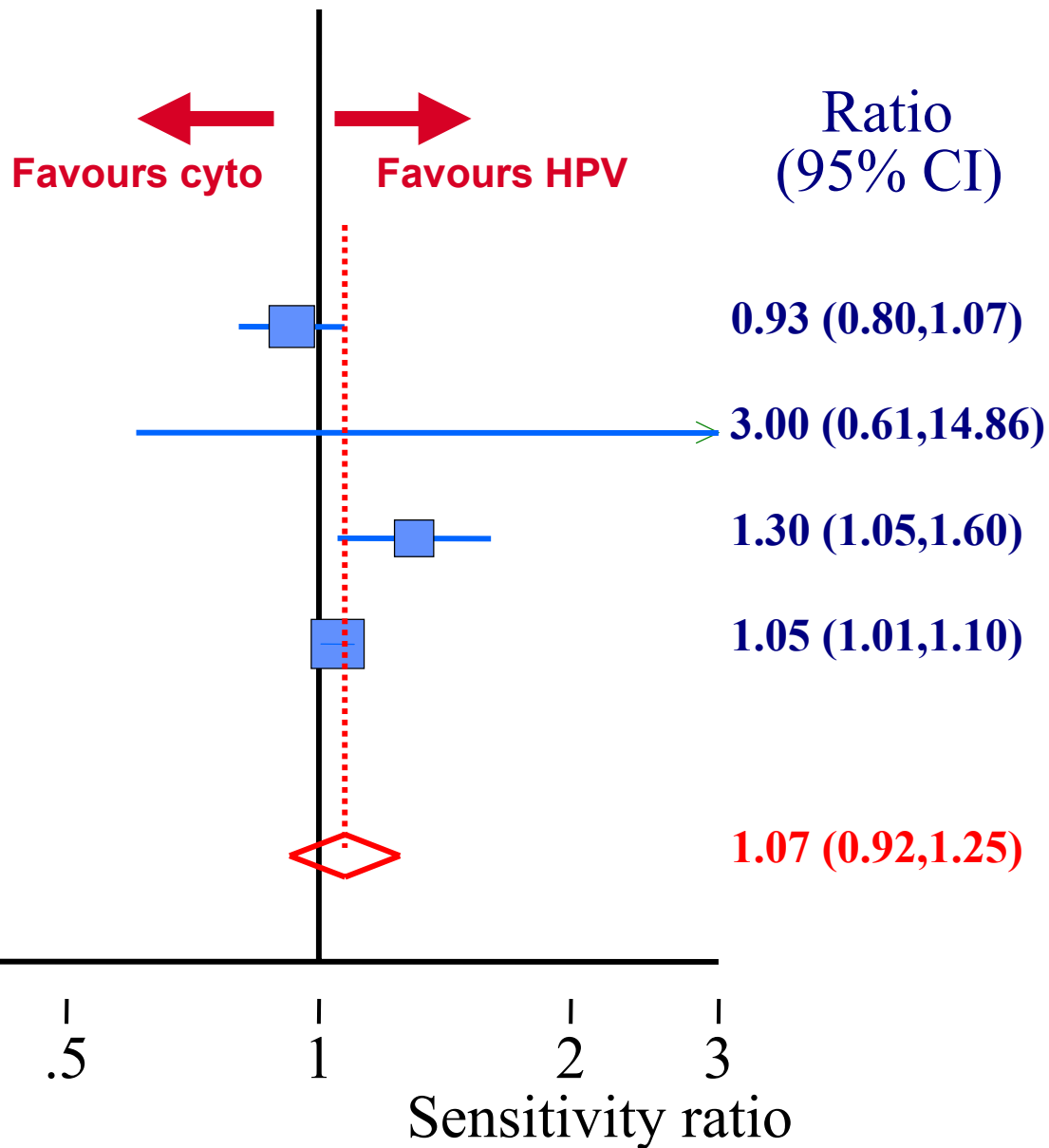
Outcome=CIN2+, pooled estimates & CI

Test Threshold	Cytology >=ASCUS 6 studies	HC2 RLU>=1 10 studies
Sensitivity	90.9 (84.3-97.4)	97.2 (95.5-99.0)
Specificity	39.7 (27.3-52.2)	28.8 (21.5-36.1)
PPV	18.8 (11.5-26.1)	27.3 (19.3-35.4)
NPV	95.3 (91.2-99.3)	98.1 (97.1-100.0)
Test+	61.4 (51.2-75.5)	77.2 (71.1-83.2)
Prevalence		19.9 (13.0-26.9)



Triage of LSIL

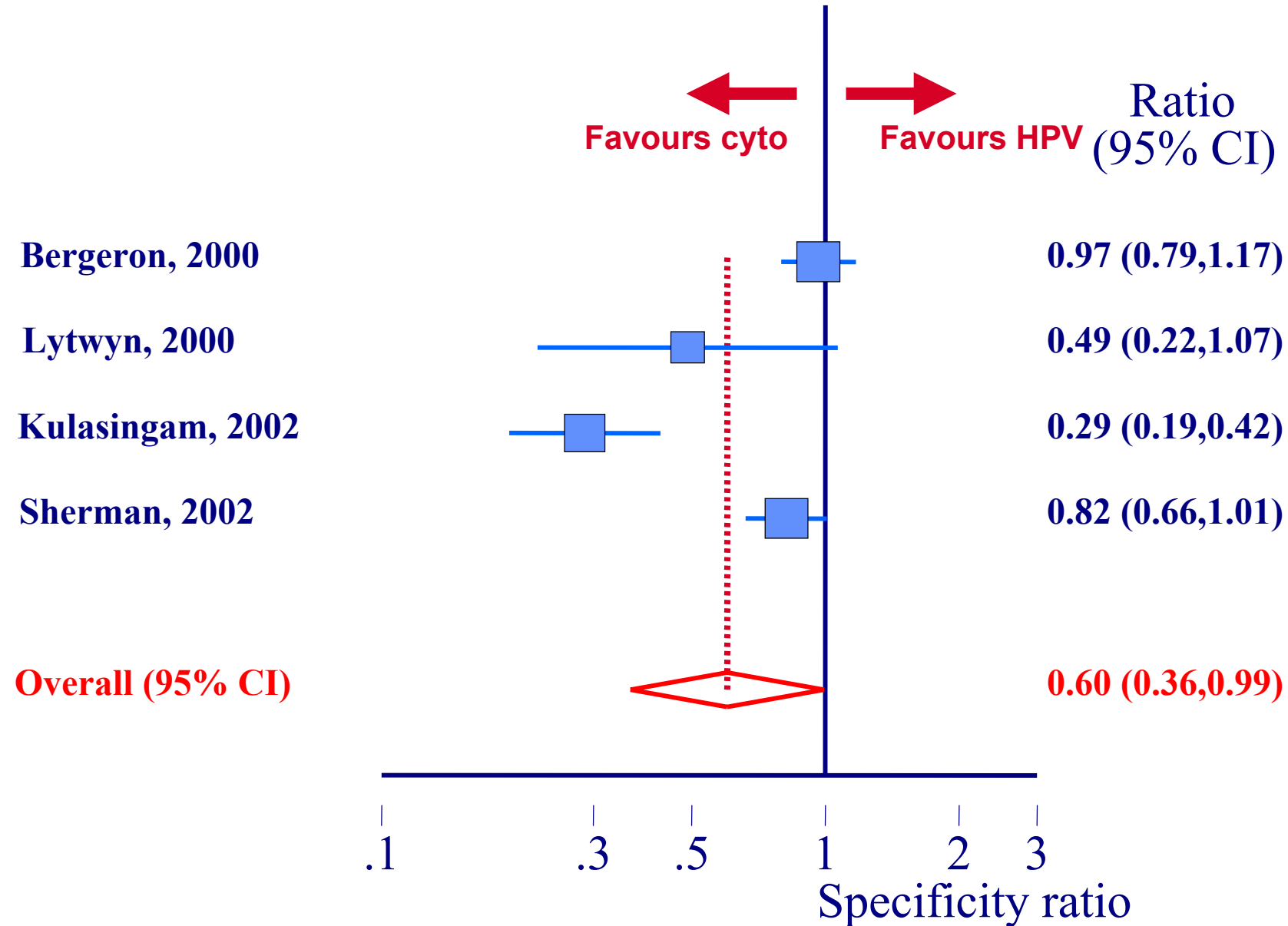
ratio of sensitivity (HC2/cytology)





Triage of LSIL

ratio of specificity (HC2/cytology)





Triage of LSIL, using a HPV RNA testing

(Pretest HPV Proofer: HPV 16,18,31,33,45)

Test	Outcome	TP	FN	FP	TN
HPV Proofer	CIN2+	4	1	1	13
GP5+/6+		4	1	10	4

	Sensitivity	Specificity	Test + rate	PPV	NPV
Proofer	80.0%	92.9%	26.3%	80.0%	92.9%
GP5+/6+	80.0%	28.6%	73.7%	28.6%	80.0%

Molden, Int J Cancer 2005



Conclusions: triage of LSIL

- **HPV DNA triage (HC2) is hardly discriminant**
 - High positivity rate
 - Inacceptably low specificity
- **More specific methods needed:**
(HPV typing, HPV specific viral load, mRNA E6/7, cell cycle proteins, ...)



Our plans: future meta-analyses

- **Finalisation EU guidelines CC screening**
- **Publication LBC**
- **Grant Cochrane Collaboration:**
 - HPV triage
 - HPV 1ary screening
 - CC screening in developing countries: VIA & VILI
 - HPV vaccination
- **Gates Foundation: individual patient data meta-analysis**
- **Collection methods for HPV testing**
- **Colposocpy**
- **P16**
- **Obstetrical/fertility outcomes after treatment of CIN**



Acknowledgements

- **Gynaecological Cancer Cochrane Collaborative Review Group**
- **European Commission:**
 - **European Cancer Network**
 - **ECCSN**