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CIN surveillance post-treatment: Cytology vs. HPV

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Background

- **Risk of progression of CIN2/3:**
 - **CIN2 to CIN3+ (24 months: 18% (CI 11-27%))** (Tainio, BMH 2018)
 - **CIN3 to cancer: >12%** (Ostor, Int J Gyn Cancer 1991)
- **Untreated CIN3: 31% risk to progress in 30y** (McCreddie, Lancet Oncol 2008)
- **Treatment of CIN2/3 is effective, nevertheless still increased risk of invasive CC up to 20 y after T** (Soutter, IJC 2005; Kalliala BMJ 2005; Strander 2007)
- **=> crucial to monitor possible treatment failure with an accurate test**

Prediction of residual/recurrent CIN after Treatment : Systematic review

- HPV vs cyto (Arbyn, Vaccine 2012, updated in 2014)
- HPV vs margins (Arbyn, Lancet Oncol 2017)
 - Inclusion criteria:
 - CIN2/3 histologically confirmed & treated
 - Margin status of excised cone and/or
 - Cytology and hrHPV testing (3-9 months post treatment)
 - Follow-up to outcome (CIN2+) for ≥ 18 months
- Number of included studies: (16 cohort; 2 case-control)
 - HPV & cytology: n=17
 - HPV & margins: n=18

Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis

Marc Arbyn, Charles W E Redman, Freija Verdoodt, Maria Kyrgiou, Menelaos Tzafetas, S

Sadaf Ghaem-Maghami, Karl-Ulrich Petry, Simon Leeson,

Christine Bergeron, Pekka Nieminen, Jean Gondry, Olaf Reich, Esther L Moss

Vaccine 30S (2012) F88–F99



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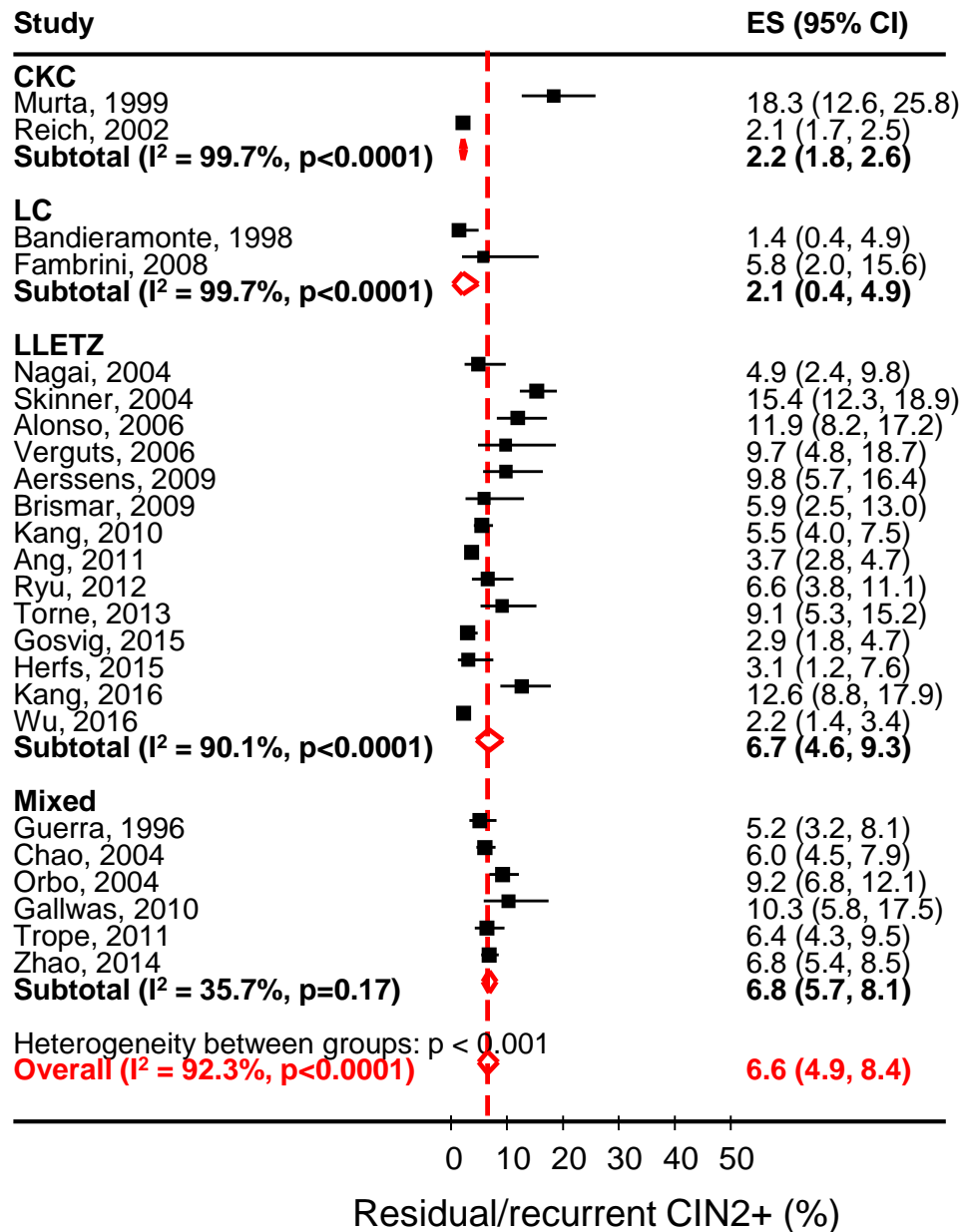


Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer

Marc Arbyn^{a,b,*}, Guglielmo Ronco^c, Ahti Anttila^d, Chris J.L.M. Meijer^e, Mario Poljak^f, Gina Ogilvie^g, George Koliopoulos^h, Pontus Nauclerⁱ, Rengaswamy Sankaranarayanan^j, Julian Peto^k

Updated in 2014

Occurrence of residual/recurrent CIN2+ (=treatment failure)



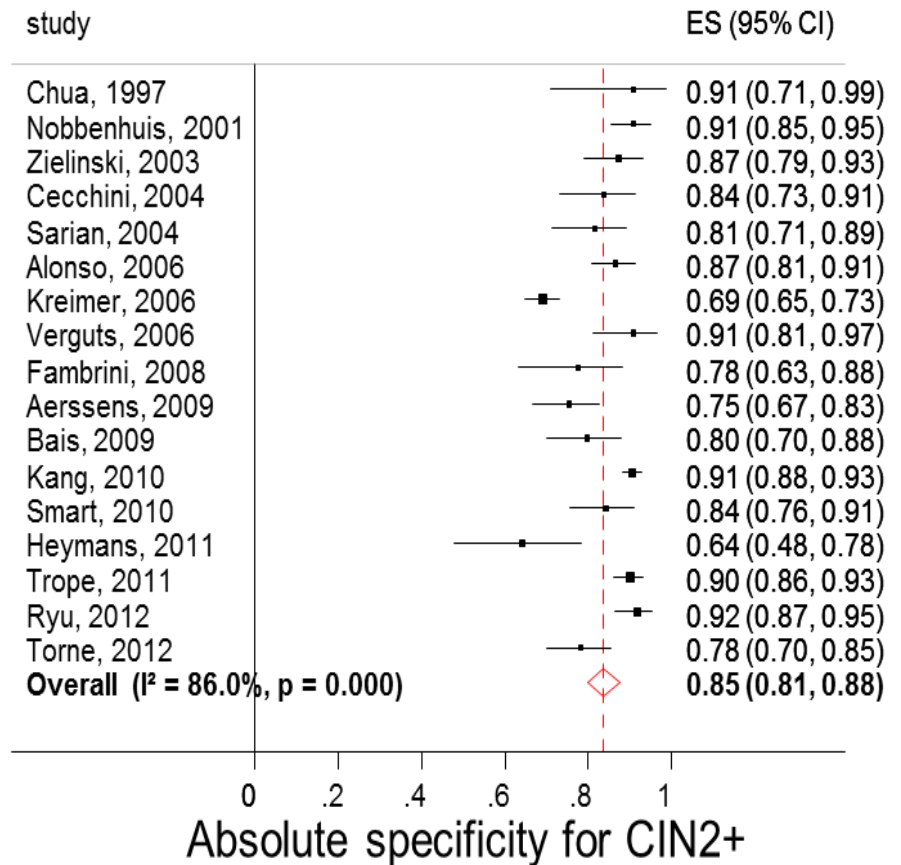
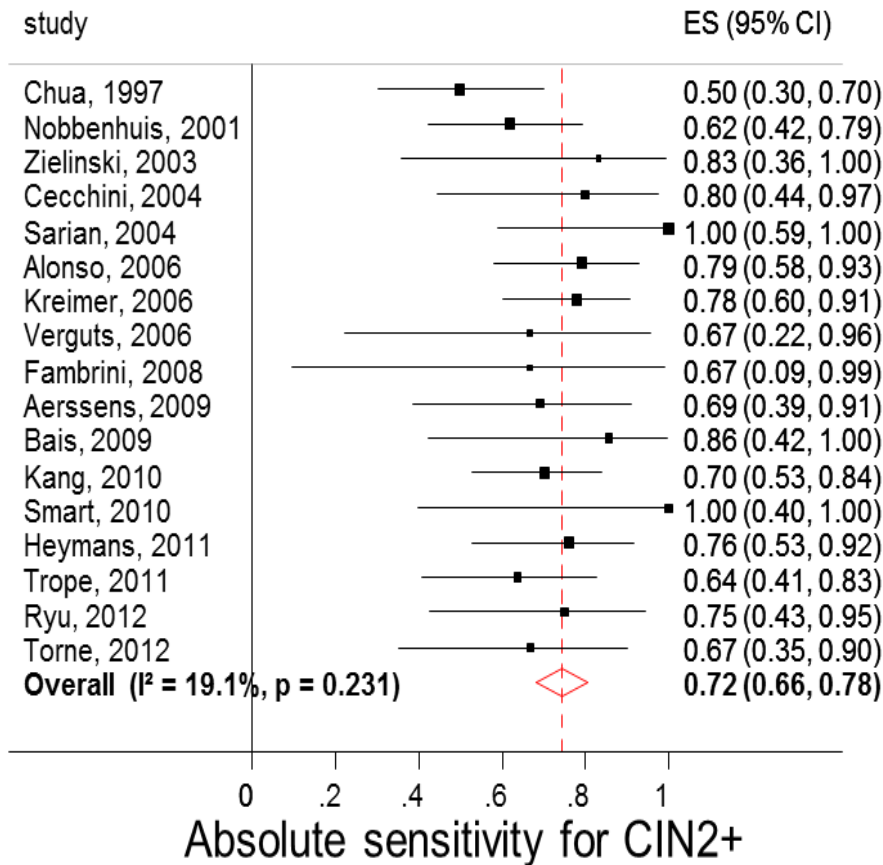
% Failure: 7%
(95% CI: 5-8%)

HPV vs cytology

Prediction of failure (CIN2+)

Follow-up cytology

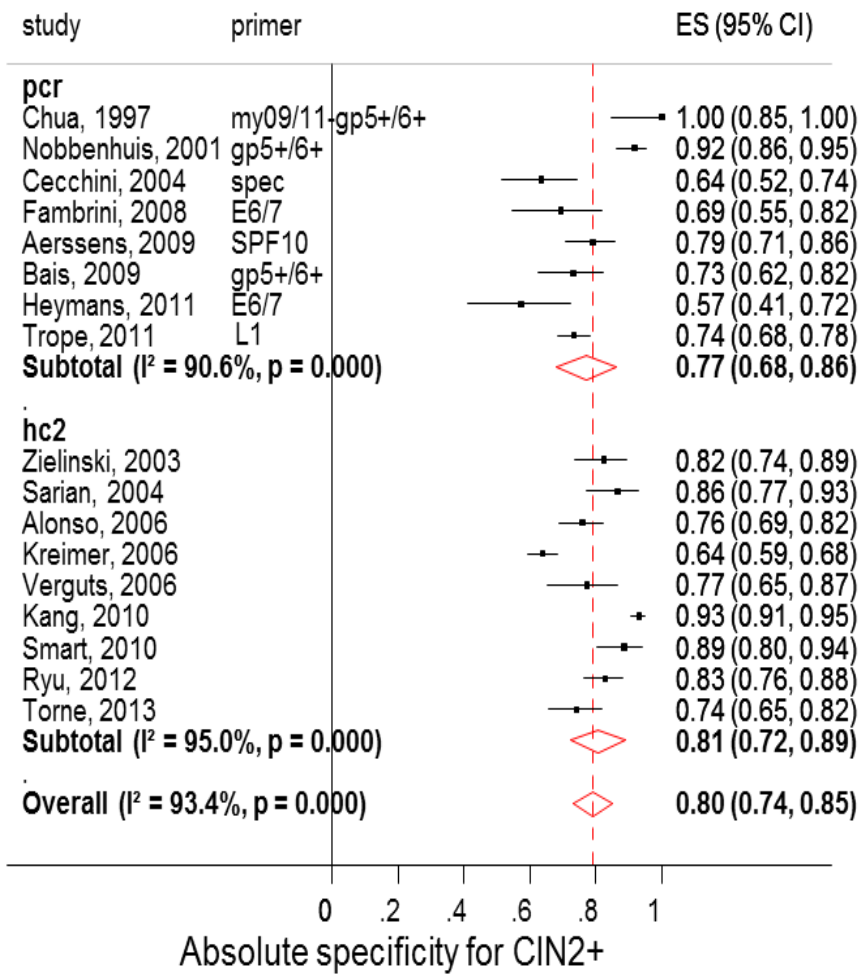
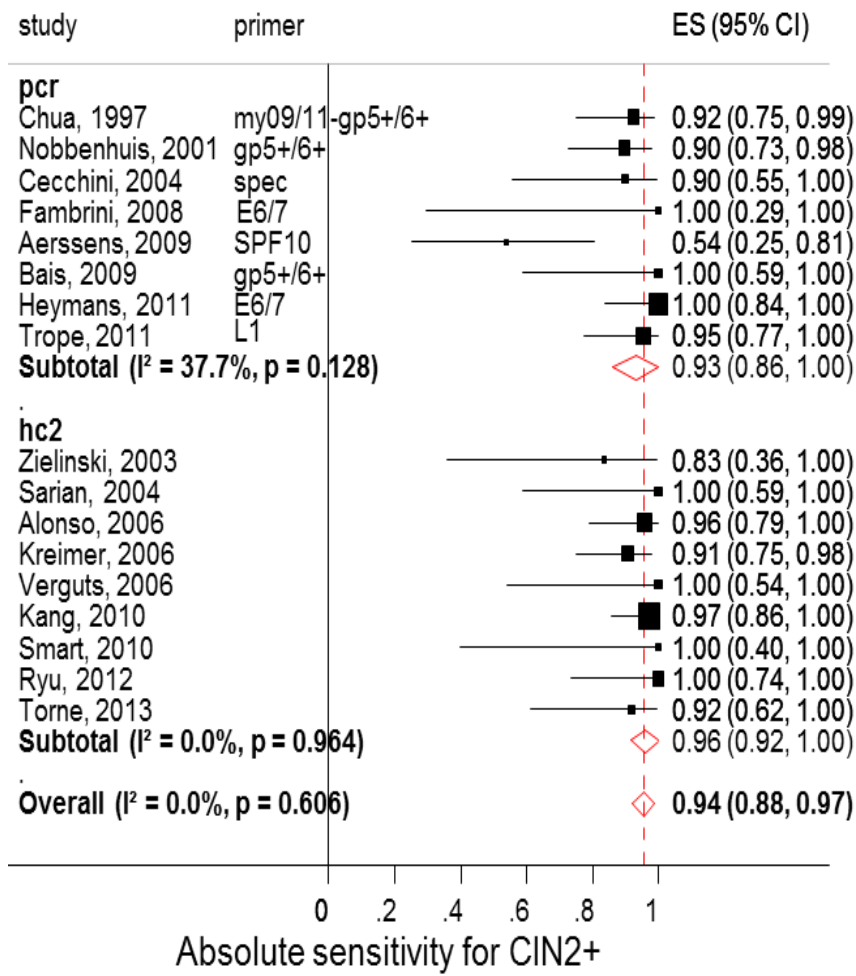
17 studies



Prediction of failure (CIN2+): follow-up cytology

HPV testing

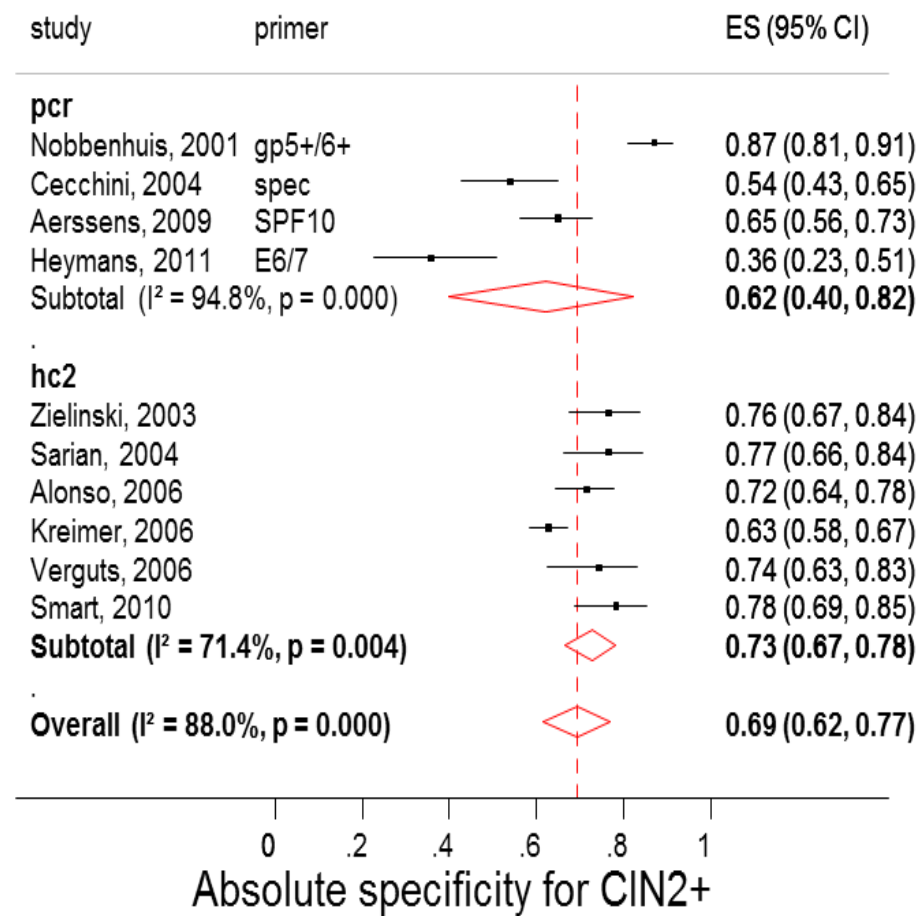
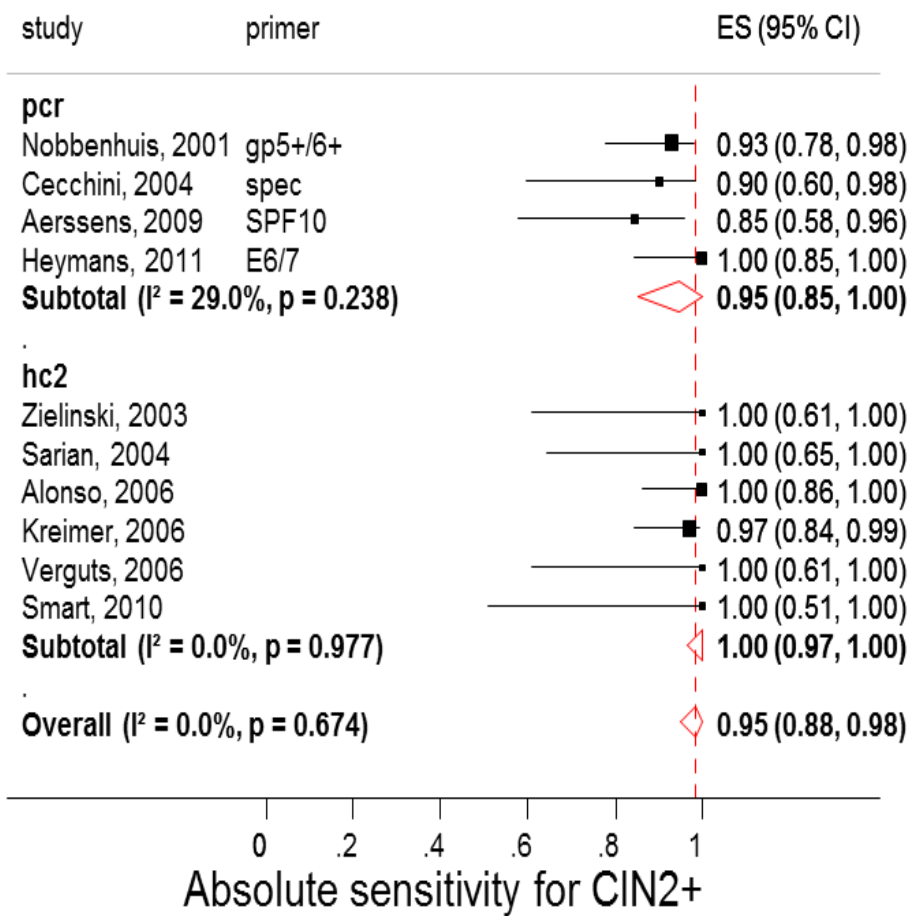
17 studies



Prediction of failure (CIN2+)

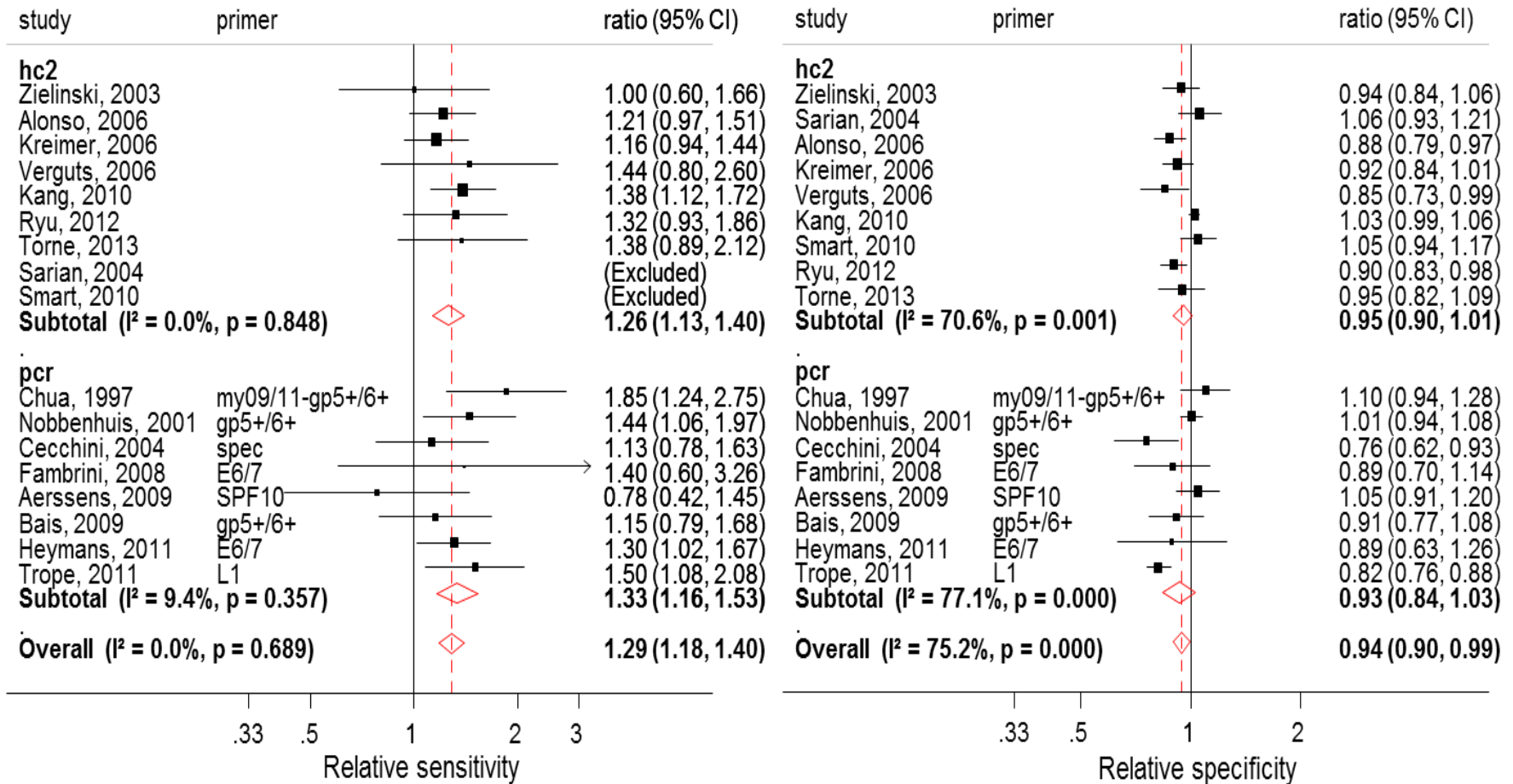
Combination HPV testing & cytology

10 studies

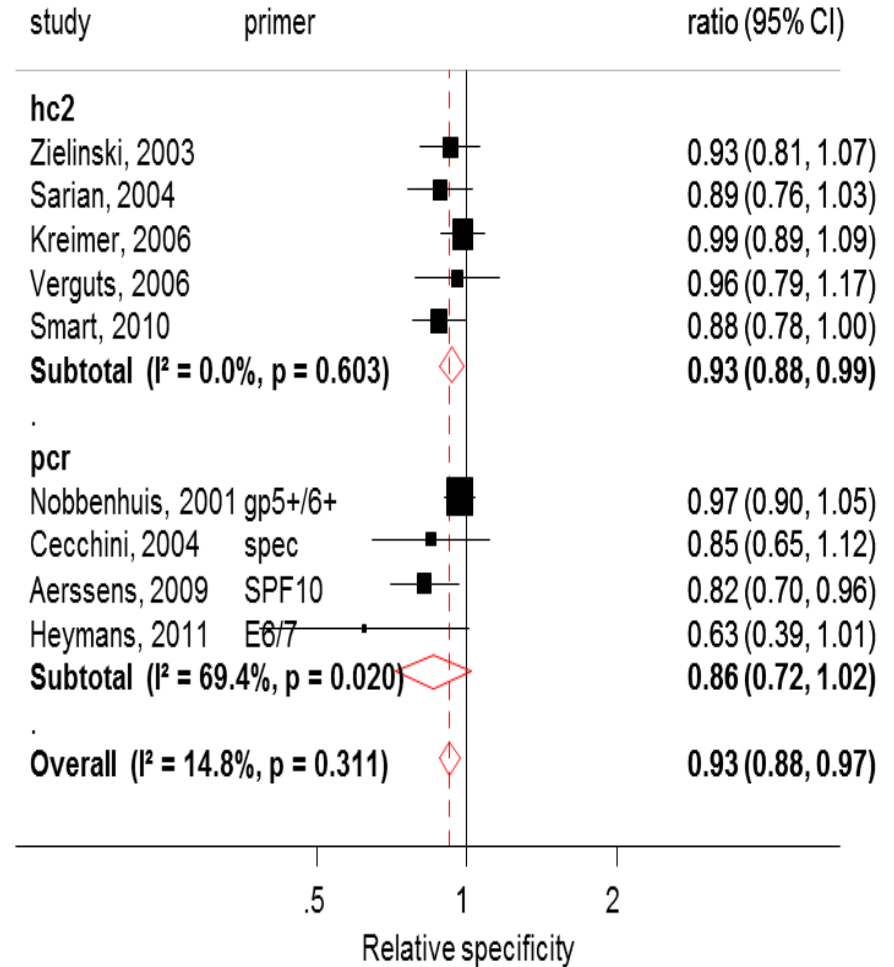
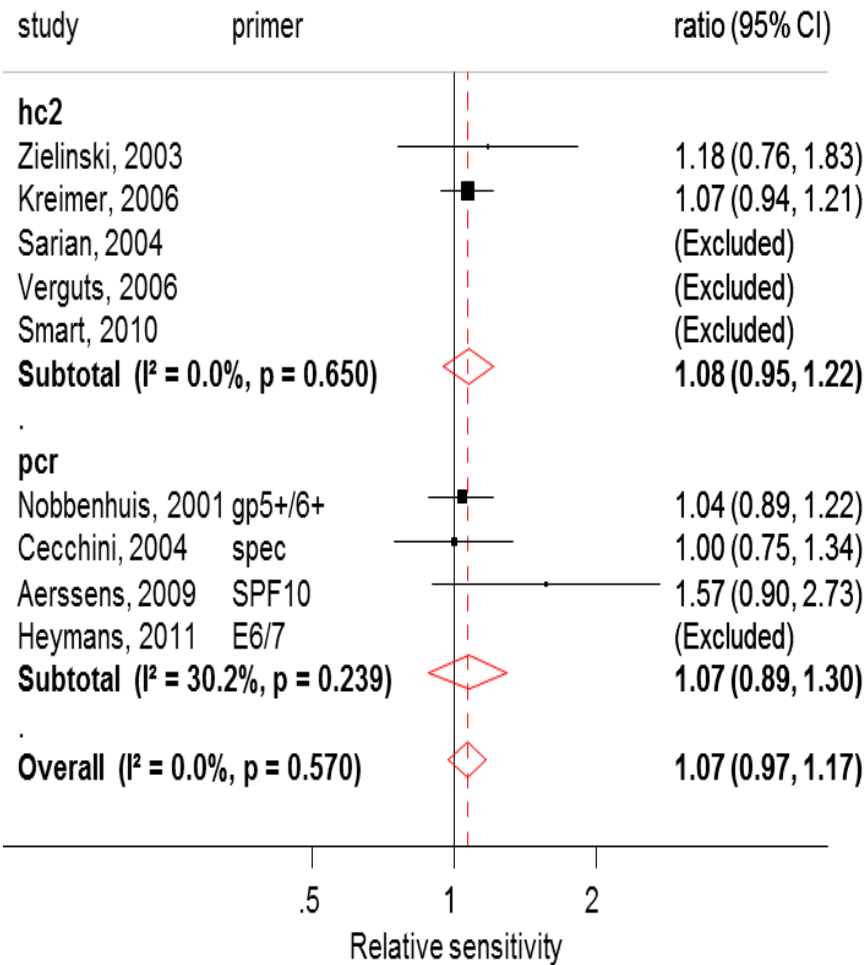


**Relative accuracy to
predict residual/recurrent CIN**

Relative sensitivity & specificity of HPV (HC2, PCR) vs cytology to predict treatment failure



Relative accuracy to detect residual/recurrent CIN2+ Combination HPV & cytology vs. HPV alone



Summary

	Sensitivity ratio		Specificity ratio	
	estimate	(95% CI)	estimate	(95% CI)
HPV / Cyto	1.29	(1.18-1.40)	0.94	(0.90-0.99)
HPV&Cyto / HPV	1.07	(0.97-1.17)	0.93	(0.88-0.97)

HPV genotyping

- Observation of persistent type-specific infection: (same type at (pre-) conisation and post-conisation)
 - Sensitivity decreases
 - Kreimer 2006: 97->77%
 - Brismar 2009: 100->60%
 - Heymans 2010: 100->100%
 - Kang 2010: 100->100%
 - Specificity and PPV increases
 - Kreimer 2006: PPV: 17->31%
 - Venturoli 2008: PPV: 67->82% (persistence HPV16/18), lower PPV gain for persistence with other types
 - Brismar 2009: PPV: 31->43%
 - Heymans 2010: 68->82%
 - Kang 2010: 93->97%
- More well designed studies needed
- Results suggest potential utility as adjunct test not as single test post treatment

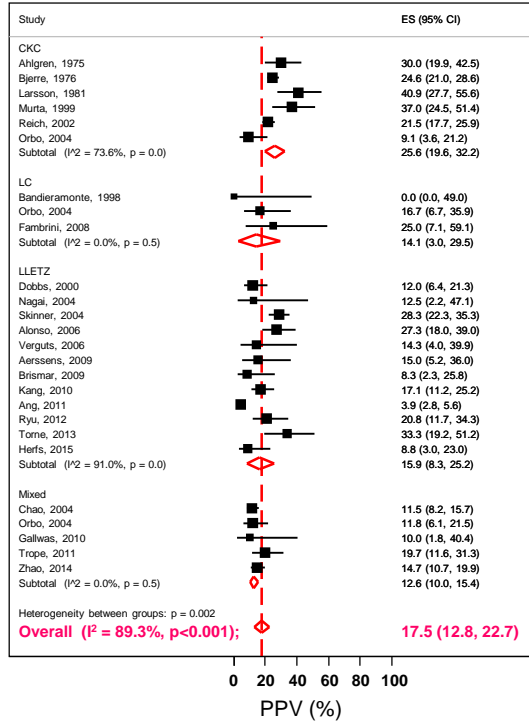
Longterm follow-up (Kocken, Lancet Oncol 2011)

- **Pooling of 3 studies (NL), over 5-21 years**
- **Follow-up cytology & hrHPV DNA at ≥ 2 time points post treatment**
- **After 3 consecutive negative cytology or 2 cotests: risk of recurrence of hgCIN = risk in population with negative cytological screening**
- **=> Recommendation: cotesting cyto & HPV at 6M & 24M**
- **But: co-testing not more sensitive than HPV testing alone**

HPV vs margins

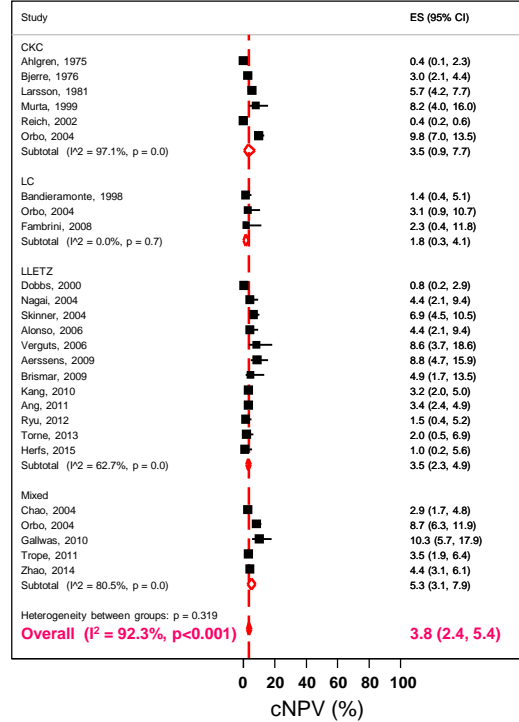
Risk CIN2+ ~ margin status

Margin+



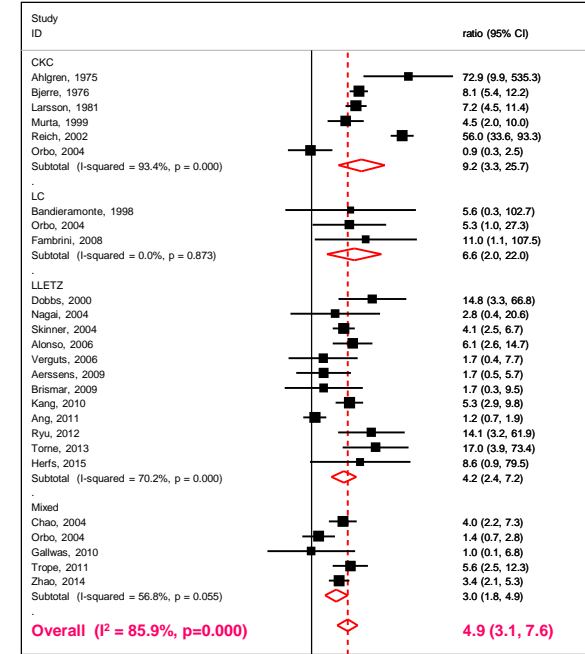
17.5%

Margin-



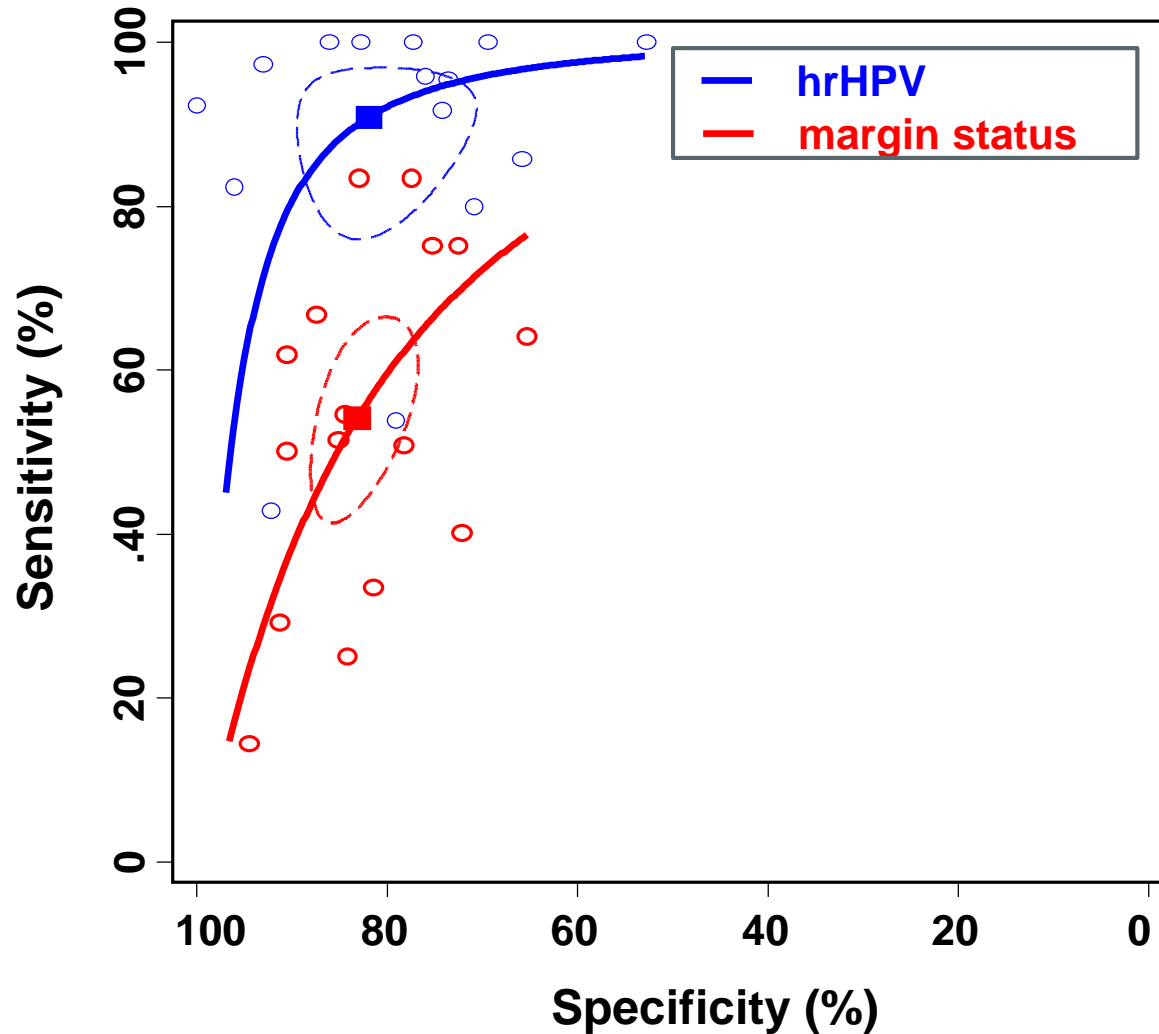
3.8%

Relative risk



4.9

Accuracy of **margin status** and **post-treatment HPV testing** to predict treatment failure

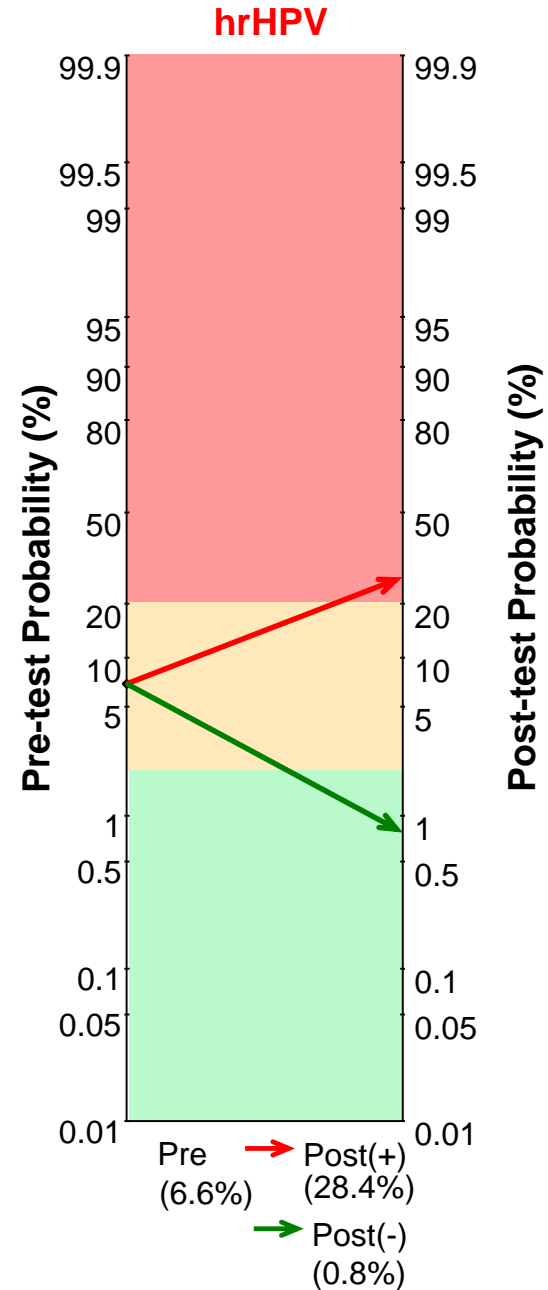
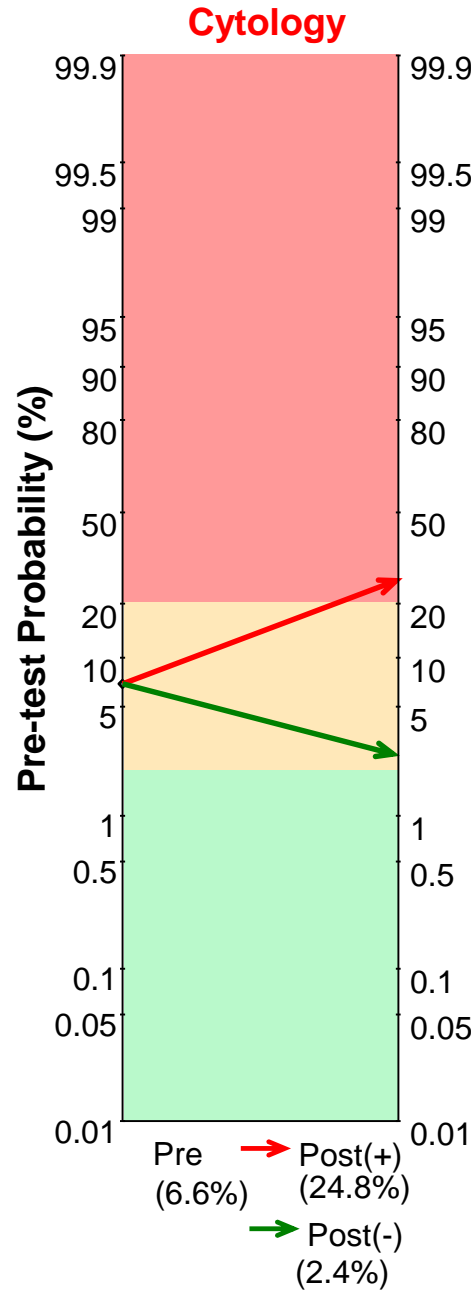
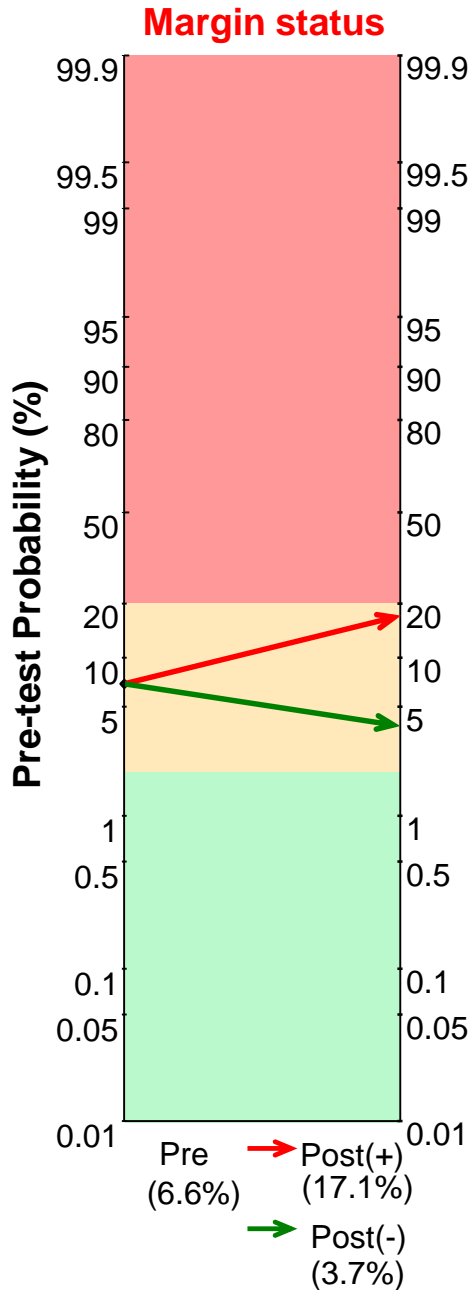


	Sensi	Speci
Margins	55.8%	84.4%
HPV	91.0%	83.8%

Accuracy of **margin status** and **post-treatment HPV testing** to predict treatment failure

	Absolute sensitivity (95% CI)	Absolute specificity (95% CI)
Margins	55.8%(45.8-65.5%)	84.4%(79.5-88.4%)
hrHPV	91.0%(82.3-95.5%)	83.8%(77.7-88.7%)
margins vs HPV	Relative sensitivity 0.62 (0.53-0.72)	Relative specificity 1.01 (0.97-1.06)

Clinical utility of tests: PPP plot (pretest-posttest probability) plot



Conclusion: prediction of cure/failure

- **Heterogeneity of studies, methods, timing of follow-up visits**
- **Women with positive margins show increased risk of treatment failure**
- **Post-treatment HPV testing: more accurate than margin status & cytology**
- **Combination cytology & HPV: slightly higher sensitivity & slightly lower specificity than HPV alone**

Conclusion: prediction of cure/failure

- **Recommended FU algorithm:**
 - **hrHPV & cytology or hrHPV alone**
 - **At 6 & 18 month**

Acknowledgements

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