RL cervixcytologie – Dient bij vrouwen met een indicatie tot cervix (cytologisch) onderzoek (P), een cytologisch onderzoek en HPV test tegelijk (I) uitgevoerd te worden in plaats van alleen cytologie (C) voor het diagnosticeren van CIN2+ om betere accuratesse (sens, spec, PPV, NPV, reproduceerbaarheid/vermindering aantal 'Gemiste" gevallen CIN2+) (O) te bereiken?

1.1 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
Bhatla et al, 2007, 2012 [1,2]	• Cross sectional study • Source of funding: department of biotechnology, government of India • Gynaecology Outpatient department, India • N=548 • Sept 2001-sept 2005	• Eligibility criteria: women with complaints of persistent vaginal discharge, intermenstrual bleeding, post-coital bleeding • Patient characteristics : median age 36 , complaints: vaginal discharge 312 (57%), intermenstrual vaginal bleeding 41 (7.5%) post-coital bleeding 18 (3.3%) • Prevalence of CIN 2+ or invasive cancer (biopsy-positive) 40 (7.8%)	• Index test(s): - HPV - Pap - HPV, pap sequential - HPV, pap smear parallel • Reference standard: biopsy or colposcopy	HPV, pap sequential (CIN2+): - Sens 96.8% (81.5-99.8) - Spec 83.6% (71.5-91.4) - PPV 75% (58.5-86.8) - NPV 98.1% (88.4-99.9) HPV, pap parallel (CIN2+): - Sens 90% (75.4-96.7) - Spec 75.6% (71.5-79.4) - PPV 23.8% (17.5-31.6) - NPV 98.9% (97.0-99.6) Pap (≥ ASCUS): -sens 77.5% (83.0-91.2) -spec 86.8% (83.9-90.1) - PPV 33.7% (24.7-44.8) - NPV 97.8% (95.8-99.0)	• No other outcomes	• Level of evidence: low • Dropouts: 36/548 (6.5%) • Results critical appraisal : Population less comparable with research question, simulation of sequential or parallel test

References
[1] Bhatla N, Mukhopadhyay A, Kriplani A, Pandey RM, Gravitt PE, Shah KV, et al. Evaluation of adjunctive tests for cervical cancer screening in low resource settings. Indian journal of cancer. 2007; 44: 51-5.
[2] Bhatla N, Puri K, Kriplani A, Iyer VK, Mathur SR, Mani K, et al. Adjunctive testing for cervical cancer screening in low resource settings. The Australian & New Zealand journal of obstetrics & gynaecology. 2012; 52: 133-9. 10.1111/j.1479-828X.2011.01402.x.

DIAGNOSIS

1.2 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
• Alaghehbandan 2013	• Observational study design (two samples taken for every patient). • No conflicts of interests reported. • Five centres in Canada. • N=331 patients • Follow-up: 1 to 3 months for new cases, and maximum of 2 years for follow-up cases	• Women 18 years of age with any grade of cytologic abnormality and who not received treatment. • Mean age: 31.2 years (SD:10.4). • 80 cases of histologically confirmed CIN 2+.	• Two cervical specimens were collected from all participants using a Cervex broom-type brush. • One was collected and suspended into PreservCyt TM collection medium (Hologic) and the second sample in SurePath medium (BD). • Cytology was performed with the PreservCyt samples using the Thin-Prep method. SurePath samples were processed via the SurePath method	**Using atypical squamous cells of undetermined Significance (ASC+) cytology:** Sensitivity to detect CIN 2+ • ThinPrep: 81.9% • SurePath: 83.7% Specificity to detect CIN 2+ • ThinPrep: 61.6% • SurePath: 66.9% False positive rate: • ThinPrep: 38.4% • SurePath: 33.1% False negative rate: • ThinPrep: 18.1% • SurePath: 16.3% Positive predictive value • ThinPrep: 43.3% • SurePath: 47.1% Negative predictive value • ThinPrep: 90.5% • SurePath: 92.1% Areas under the curve for ThinPrep (0.717) and SurePath (0.754) are very similar.	Rate of unsatisfactory specimens: • ThinPrep: 16 (4.8%) • SurePath: 0	Critical appraisal has been conducted with the QUADAS-II instrument. Quality of evidence is considered high. Only downgrade would possible on the lack of details regarding the interpretation of the reference standard, however, this is not considered a crucial aspect for our clinical question. [level of evidence: 3 – due to one study].

Prior knowledge of HPV status and cytology sensitivity and specificity.

STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
• Benoy et al, 2011[1]	• Prospective study • Source of funding: Belgian Foundation Against Cancer, European commission (ECCG project) • No CoI • N= 2905 • Aug 2005-Feb 2007	• Eligibility criteria: women that visited gynaecologists for routine health checks. Exclusion pregnancy and history of cervical disease (previous CIN2+) • Patient characteristics: median age 42.7 19.3%<30 y • Prevalence of CIN2+: 46/2905 (1.6%)	• Index test: with or without prior knowledge of HPV status • Reference standard: Colposcopy	• With prior knowledge: -sens 36/46(76.1%) -spec 2675/2859 (93.9%) • Without prior knowledge: -sens 27/46 (58.7%) -spec 2699/2859 (94.4%)	• No other outcomes	• Level of evidence: High • No drop outs • Clear definition of positive/negative cases, all patients in analysis, follow up period of 24 months to detect CIN2+
• Bergeron et al, 2015[2]	• Nested study in RCT • Source of funding: RCT was funded by European Union, Italian Ministry of Health, Associazione Italiana per la Ricerca sul Cancro • No CoI • N=1261 • Feb 2002- Dec 2004	• Eligibity criteria: women age 25 to 60 who were not pregnant, had never undergone hysterectomy, had not been treated for CIN the last 5 years and who were attending for a new routine cervical screening episode. • Patient characteristics: no information • Prevalence of CIN2+, after follow up: 3.7%	• Index test: with knowledge of HPV status • Reference standard: Colposcopy	• With prior knowledge of HPV status: During recruitment and follow up CIN2+ -sens 110/139 (79.1%) -spec 756/1122 (67.4%)	• Relative sensitivity vs stand alone blind cytology if only HPV-positive women with ASCUS+ informed cytology were referred to colposcopy and had postcolposcopy follow up was 2.20 (95% CI 1.52-3.17) for CIN2+	• Level of evidence: High • No drop outs • Clear definition of positive/negative cases, all patients included in analysis, follow up period median duration 1099 days.

References

[1] Benoy IH, Vanden Broeck D, Ruymbeke MJ, Sahebali S, Arbyn M, Bogers JJ, et al. Prior knowledge of HPV status improves detection of CIN2+ by cytology screening. American journal of obstetrics and gynecology. 2011; 205: 569.e1-7. 10.1016/j.ajog.2011.06.101.
[2] Bergeron C, Giorgi-Rossi P, Cas F, Schiboni ML, Ghiringhello B, Dalla Palma P, et al. Informed cytology for triaging HPV-positive women: substudy nested in the NTCC randomized controlled trial. Journal of the National Cancer Institute. 2015; 107: Pmc4339260.

DIAGNOSIS

Bij vrouwen met een indicatie voor cytologische screening, geeft SurePath een betere sensitiviteit, specificiteit voor de detectie van CIN2+ dan ThinPrep?

1.3 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
• Alaghehbandan 2013	• Observational study design (two samples taken for every patient). • No conflicts of interests reported. • Five centres in Canada. • N=331 patients • Follow-up: 1 to 3 months for new cases, and maximum of 2 years for follow-up cases	• Women 18 years of age with any grade of cytologic abnormality and who not received treatment. • Mean age: 31.2 years (SD:10.4). • 80 cases of histologically confirmed CIN 2+.	• Two cervical specimens were collected from all participants using a Cervex broom-type brush. • One was collected and suspended into PreservCyt TM collection medium (Hologic) and the second sample in SurePath medium (BD). • Cytology was performed with the PreservCyt samples using the Thin-Prep method. SurePath samples were processed via the SurePath method	**Using atypical squamous cells of undetermined Significance (ASC+) cytology:** Sensitivity to detect CIN 2+ • ThinPrep: 81.9% • SurePath: 83.7% Specificity to detect CIN 2+ • ThinPrep: 61.6% • SurePath: 66.9% False positive rate: • ThinPrep: 38.4% • SurePath: 33.1% False negative rate: • ThinPrep: 18.1% • SurePath: 16.3% Positive predictive value • ThinPrep: 43.3% • SurePath: 47.1% Negative predictive value • ThinPrep: 90.5% • SurePath: 92.1% Areas under the curve for ThinPrep (0.717) and SurePath (0.754) are very similar.	Rate of unsatisfactory specimens: • ThinPrep: 16 (4.8%) • SurePath: 0	Critical appraisal has been conducted with the QUADAS-II instrument. Quality of evidence is considered high. Only downgrade would possible on the lack of details regarding the interpretation of the reference standard, however, this is not considered a crucial aspect for our clinical question. [level of evidence: 3 – due to one study].

DIAGNOSIS

Bij Patienten die in aanmerking komen voor screening en op indicate voor cervixytologie (P) geeft het gebruik van een Computer Ondersteunende screening (I) (=ThinPrep Imaging System van Hologenic Of FocalPoint Slide Profiler van Becton en Dickinson Diagnostics) vergeleken met manuele screening een betere diagnostische accuratesse van afwijkingen?

1.4 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results outcome	VI Critical appraisal of study quality
• Biscotti et al, 2005[1]	• Observational study • Supported by Cytyc • USA, 4 labs • N= 9,550 • Dec 2000 and Jul 2001	• Specimens were collected for clinical study from routine clinical volume at the participant's lab	ThinPrep Imager Vs Manual reading	Detecting ASCUS+: Manual Sensitivity: 75.6 (72.2-78.8) Specificity: 97.6 (97.2-97.6) Imager Sensitivity: 82.0 (78.8-84.8) Specificity:97.8 (97.4-98.1) Detecting HSIL+: Manual Sensitivity: 74.1 (66.0-81.2) Specificity: 99.4 (99.2-99.6) Imager Sensitivity: 79.9 (72.2-86.2) Specificity:99.6 (99.5-99.7)	reference test was only done on a random sample of negative cases
• Colgan et al, 2013[2]	• Observational study • No CoI • Ontario, Canada • N= 10,233 • 2008	• All samples were taken from women of any age.	FocalPoint Guided Screening Vs Manual reading	Detecting ASC-US+: Manual: Sensitivity: 93.1 Specificity: 98.2 FocalPoint Guided Screening: Sensitivity: 85.9 Specificity: 96.8	reference test was only done on discordant pairs
• Heard et al, 2013[3]	• Observational study • No CoI reported • UK • N=15,846 • •	• Samples from routine primary screening	ThinPrep Imager Vs Routine cytology	Detecting abnormalities (no further definitions) ThinPrep Imager Sensitivity 80.3 (78.5-81.9) Specificity 98.0 (97.9-98.2) Routine cytology Sensitivity 78.9 (77.1-80.6) Specificity 98.2 (97.9-98.4)	reference test only on positive or discordant cases
• Kitchener al, 2011b[4]	• RCT MAVARIC • Funding: National Institute for Health Research Health Technology assessment	• Cervical samples from women aged 25-64 years were obtained during routine primary cervical screening as part of the national	ThinPrep Imager Vs Manual reading	Detecting CIN2+ Relative sensitivity 0.92 (95% CI 0.89-0.95) Relative specificity 0.6% (95% CI 0.5-0.7)	reference standard only for positive index test cases

	Programme • UK • N= 48,271 • March 2006 and Feb 2009 • ISRCTN66377374	screening programme			
• Klug et al, 2013[5]	• RCT • Grant from Hologenic and The Professional Association of Gynecologists • Multicentre, Mainz, Germany • N=11,576 • Aug 2007 to March 2009 •	• Women 20 years of aged or older who visited 1 of 20 office-based gynecology practices to undergo screening for cervical cancer and its precursor lesions.	Liquid based cytology and ThinPrep Imager vs Liquid based cytology and manual reading	Detecting CIN2+ Positive predictive value: LBC and ThinPrep 73% (61-82) LBC and Manual 72% (60-83) Unsatisfactory by ThinPrep Imager: 2.86% Unsatisfactory by manual reading: 0.31%	reference standard only for positive index test cases
• Koltz et al, 2013[6]	• Observational study • No CoI • USA • N=70,522 • July 2006-june 2007 • Follow up until 2010	• Samples from routine screening	ThinPrep Imager Vs Manual	Detecting ASC-H Relative sensitivity 0.74 Relative specificity 0.43 Detecting HGSIL Relative sensitivity 0.97 Relative specificity 0.85	
• Palmer et al, 2013[7]	• RCT • Hologenic supported travel to Hologenic annual Medical Education Meeting • Scotland • N=169,917 • 2008	• Samples from screening programme	ThinPrep Imager vs Manual	Detecting any grade of abnormality ThinPrep Imager Sensitivity 94.6 (94.0-95.1) Specificity 95.6 (95.4-95.7) Manual Sensitivity 94.3 (93.8-94.8) Specificity 94.9 (94.7-95.0) Detecting CIN2+ Thin Prep Imager Positive predictive value 80.7% (78.5-82.9) Manual Positive predictive value 78.5% (76.7-80.3)	reference standard only for positive index test cases

ASC-H atypical squamous cells high-grade ASCUS atypical squanmous cells of undetermined signifance, CoI conflict of Interest, CIN cervical intraepithelial neoplasm, HG-SIL or HSIL high-grade squamous intraepithelial lesion, LBC liquid based cytology, RCT randomized controlled trial

[1] Biscotti CV, Dawson AE, Dziura B, Galup L, Darragh T, Rahemtulla A, et al. Assisted primary screening using the automated ThinPrep Imaging System. American journal of clinical pathology. 2005; 123: 281-87.
[2] Colgan TJ, Bon N, Clipsham S, Gardiner G, Sumner J, Walley V, et al. A validation study of the focalpoint gs imaging system for gynecologic cytology screening. Cancer Cytopathology. 2013; 121: 189-96.
[3] Heard T, Chandra A, Culora G, Gupta SS, Herbert A, Morgan M. Use of the thinprep imaging system for internal quality control of cervical cytology. Cytopathology : official journal of the British Society for Clinical Cytology. 2013; 24: 246-53.
[4] Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, et al. Automation-assisted versus manual reading of cervical cytology (MAVARIC): A randomised controlled trial. The Lancet Oncology. 2011; 12: 56-64.
[5] Klug SJ, Neis KJ, Harlfinger W, Malter A, Konig J, Spieth S, et al. A randomized trial comparing conventional cytology to liquid-based cytology and computer assistance. International Journal of Cancer. 2013; 132: 2849-57.
[6] Koltz BR, Russell DK, Lu N, Bonfiglio TA, Varghese S. Effect of thin Prep® imaging system on laboratory rate and relative sensitivity of atypical squamous cells, high-grade squamous intraepithelial lesion not excluded and high-grade squamous intraepithelial lesion interpretations. CytoJournal. 2013; 10.
[7] Palmer TJ, Nicoll SM, McKean ME, Park AJ, Bishop D, Baker L, et al. Prospective parallel randomized trial of the multicyte(trademark) thinprep(registered trademark) imaging system: The scottish experience. Cytopathology : official journal of the British Society for Clinical Cytology. 2013; 24: 235-45.

DIAGNOSIS

Bij patiënten met indicatie tot follow up wegens behandeling van dysplasie wat is de specificiteit/ sensitiviteit/ PPV/ NPV voor CIN2+ van self-sampling vergeleken met sampling door een clinicus?

1.5 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcomes	VII Critical appraisal of study quality
• Taylor et al, 2011[1]	• Randomised controlled trial • Grants: Bill and Melinda Gates Foundation and Cancer Association of South Africa reported. • South Africa • N= 2670 women of which 812 treated • Follow-up visit 6 and 12 months • June 2000-Dec 2002	• Women aged 35-65 years, no history of hysterectomy, no prior treatment for CIN • Mean age: 43.4 years (SD:7.1). • 124 cases of histologically confirmed CIN 2+.	• HPV testing: Hybrid Capture 2 • Cytology: -Liquid based cytology -Conventional Papanicolaou cytology • Biopsy (reference standard)	**Cryotherapy-treated women at 6/12 months** -HPV testing (biopsy confirmed CIN2+) Self-collected samples Sens 54.6 (38.0-70.2) Spec 63.8 (60.4-67.1) PPV 6.4 (3.5-9.2) NPV 96.9 (95.4-98.5) Clinician-collected samples Sens 84.9 (69.1-93.4) Spec 73.2 (70.0-76.2) PPV 12.8 (8.3-17.3) NPV 99.1 (98.3-99.9) - Cytology (clinician-collected samples) ASCUS+ Sens 75.8 (59.0-87.2) Spec 78.8 (75.8-81.6) PPV 14.2 (9.0-19.4) NPV 98.7 (97.7-99.6) LSIL+ Sens 54.6 (38.0-70.2) Spec 90.8 (88.5-92.6) PPV 21.3 (12.5-30.1) NPV 97.8 (96.7-98.9)	-	Critical appraisal has been conducted with the QUADAS-II instrument. Quality of evidence is considered high. However cryotherapy is not a common therapy in the Netherlands.

CIN cervical intraepithelial neoplasia, HPV human pappiloma virus PPV positive predictive value, NPV negative predictive value

[1] Taylor S, Wang C, Wright TC, Denny L, Kuhn L. A comparison of human papillomavirus testing of clinician-collected and self-collected samples during follow-up after screen-and-treat. International journal of cancer Journal international du cancer. 2011; 129: 879-86. 10.1002/ijc.25731.

DIAGNOSIS FOLLOW –UP

bij patiënten die niet behandeld zijn voor CIN dient in de follow up een co-test versus cytologie gedaan te worden om CIN2+ te diagnosticeren?

1.6 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Critical appraisal of study quality
• Gosvig et al 2015	• **Design:** observational • **Conflict of interest:** Some reported • **Setting:** Denmark • **Sample size:** 588 • **Duration:** Oct 2002- March 2005, follow up 24 months. • **Protocol:** none reported •	• **Eligibility criteria:** women with CIN2+ scheduled for conization **Reference test:** pathology report form routine screening	• Cytology vs • Cytology+hrHPV (HCII)	Accuracy for detecting CIN2+ at first follow up (4–6 months) **Cytology** • Sensitivity: 81.0 (95%-CI: 58.1–94.6) • Specificity: 85.2 (95%-CI: 82.0-88.0) • PPV: 16.8 (95%-CI: 10.1–25.6) • NPV: 99.2 (95%-CI: 97.6–99.8) **Cytology and HPV test** • Sensitivity: 95.2 (95%-CI:76.2-99.9) • Specificity: 73.2 (95%-CI: 69.3–76.8) • PPV: 11.6 (95%-CI: 7.3–17.4) • NPV: 99.8 (95%-CI: 98.7-100.0)	• Niveau A1
• Tan et al 2013	• **Design:** observational study • **Conflict of Interest:** None reported • **Setting:** royal Women's hospital Melbourne, Australia • **Sample size:** 985 • **Duration:** May 2001-june 2005 Follow up : 2 years • **Protocol:** none reported	• **Eligibility criteria:** Women undergoing ablative or excisional treatment for CIN2+ • **Patient characteristics:** Mean age 27.9 years (range 15-60); smoking 477/985 (48.4%) • **Reference test:** Colposcopy	• Cytology vs • Cytology and hrHPV (HCII)	Accuracy for detecting CIN2 or 3 Visit 1 (6 months) **Cytology:** • Sensitivity: 78 (95%-CI:40-97) • Specificity: 94 (95%-CI: 90-96) • PPV: 30 (95%-CI: 13-53) • NPV: 99 (95%-CI: 97-100) **Cytology and hrHPV test:** • Sensitivity: 100 (95%-CI:59-100) • Specificity: 75 (95%-CI: 69–81) • PPV: 11 (95%-CI: 5-22) • NPV: 100 (95%-CI: 98-100) Visit 2 (12 months) **Cytology:** • Sensitivity: 43 (95%-CI:10-82)	Niveau A2

				• Specificity: 94 (95%-CI: 92-96) • PPV: 8 (95%-CI: 2-21) • NPV: 99 (95%-CI: 98-100) **Cytology and hrHPV test:** • Sensitivity: 67 (95%-CI:22-96) • Specificity: 80 (95%-CI: 76–83) • PPV: 4 (95%-CI: 1-9) • NPV: 100 (95%-CI: 98-100) Visit 3 (24 months) **Cytology:** • Sensitivity: 100 (95%-CI:59-100) • Specificity: 97 (95%-CI: 95-98) • PPV: 28 (95%-CI: 12-49) • NPV: 100 (95%-CI: 99-100) **Cytology and hrHPV test:** • Sensitivity: 100 (95%-CI:59-100) • Specificity: 82 (95%-CI: 78–85) • PPV: 7 (95%-CI: 3-14) • NPV: 100 (95%-CI: 99-100)	

CIN cervical intraepithelial neoplasia, HC hybrid capture, HR HPV high-risk human papillomavirus

1.7 SYSTEMATIC REVIEWS

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Critical appraisal of review quality
• Kocken et al. 2012	• **Design:** systematic review with meta-analysis • **Conflict of interest:** none reported • **Search date:**April 2011 • **Searched databases:**Pubmed Medline, Embase, Cochrane Library, WHO International Clinical Trial database • **Included study design:** all • **Number of included**	**Eligibility criteria:** prospective and retrospective studies: women treated for CIN2/3 by either conization (laser or cold-knife) or LLETZ. Follow up: hrHPV testing, cytology, and/or co-testing at six months after treatment; Positive endpoint disease histologically defined, Negative endpoint histologically defined or a re-petitive negative cytological test result.	• Cytology Vs • Cytology and hrHPV	• Accuracy for detecting CIN2+ at 6 months follow up: **Cytology** • Pooled sensitivity: 79 (95%-CI:72-85) • Pooled Specificity: 81 (95%-CI: 74-86) **Cytology and HPV test** • Pooled sensitivity: 95 (95%-CI:91-98) • Pooled specificity: 67 (95%-CI: 60– 74)	• Quality 8/11 according to AMSTAR

	studies: 8 • **Protocol existence reported:**no				

LLetz Loop Excision of the Transformation Zone