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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

CERVICAL CANCER SCREENING PROGRAM AND HUMAN PAPILLOMAVIRUS (HPV) TESTING, PART II: UPDATE ON HPV PRIMARY SCREENING

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HEALTH TECHNOLOGY ASSESSMENT

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- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AGC	atypical glandular cells
AR	attitbutable risk
ARexp	attitbutable risk among exposed subjects
ARpop	attitbutable risk in the population
ASC-H	atypical squamous cells where presence of HSIL cannot be excluded
ASC-US	atypical squamous cells of undetermined significance
BSCC	Belgian Society for Clinical Cytology
Ca	cancer
CI	95% confidence interval
CIB	confidence interval bound
CIN	cervical intra-epithelial neoplasia
df	degrees of freedom
DNA	deoxyribonucleic acid
FIGO	International Federation of Gynaecology and Obstetrics
GP	general practitioner
HPV	Human papilloma virus
hrHPV	high risk HPV type
HSIL	high-grade squamous intraepithelial lesions
ICER	incremental cost-effectiveness ratio
IMS	Intercontinental Marketing Services
lcib	lower confidence interval bound
LSIL	low-grade squamous intraepithelial lesions
LY	life year
NILM	negative for intraepithelial lesions or malignancy
OR	odds ratio
PCR	polymerase chain reaction
RR	relative risk
ucib	upper confidence interval bound

VVOG	Vlaamse Vereniging voor Obstetrie en Gynaecologie

SCIENTIFIC REPORT

1 OPTIMAL FIRST SCREENING TEST

1.1 Update on accuracy of HPV vs. cytology screening

1.1.1 Introduction

The organization and implementation of preventive healthcare, in which cancer screening is part of, is dedicated to the communities (state reform of 1980). In line with this decentralization of care towards the more regional levels, we will describe the organization of cervical cancer screening per region. In this section we will focus on the organizational aspects of screening.

1.1.1.1 Flemish region

The Flemish region is the only region where a formal cervical cancer screening program has been set up.

The historical context and the current situation in the Flemish region are in detail described in a recent report of the working group on cervical cancer screening[1], in preparation of the health conference on cancer screening programs, held in December 2013. This section will only summarize the main characteristics of the current screening program.

Since June 2013 the organized cervical cancer screening program (in line with the recommendations of the World Health Organization and the European Union) has started and women between 25 and 64 years were invited for a PAP smear test, once every 3 years. The eligible women receive an invitation by mail (send by the Centre for Cancer Detection-Centrum voor Kankeropsporing) with an information leaflet on the advantages and disadvantages of cervical cancer screening and the encouragement to make an appointment with their GP or gynecologist. The physician performs a PAP smear test and sends the specimen to one of the recognized laboratories (see further on the licensing of laboratories). The test results are gathered in a centralized cyto-histo-pathology register by the Belgian Cancer Registry (Stichting Kankerregister-Fondation Registre du Cancer). This register serves as the centralized information source for the call-recall system, which is organized by the Centre for Cancer detection (Centrum voor Kankeropsporing). The Flemish working group on cervical cancer screening (Vlaamse werkgroep Bevolkingsonderzoek naar baarmoederhalskanker)

co-supervises the enrollment of the cervical cancer screening program and advises the Flemish minister of Health Affairs on the performance of this screening program.

In contrast to the Flemish breast cancer screening program, this screening program is restricted to the organization of the call-recall system of the eligible women. No active guidance and quality control is provided for the test and analysis procedure. This current shortage leads to a variety in practices between clinicians and between laboratories (see further in section on quality control systems). Within the screening program, no feedback towards the GPs and gynecologists on the quality of the PAP smear tests is provided.

The call-recall system itself is also susceptible for missing eligible women. Any delay in data transfer between the laboratories and the BCR, leads to a delay in the completion of the list of screened women, which is used by the CvKO to refine the call-recall system. In the invitation letter no particular moment and place for screening is mentioned and the women is obliged to plan herself an appointment with a GP or gynecologist, which makes this system of invitation itself susceptible to exclude certain women of the screening program.

Insufficient knowledge about the effect of the letter and the additional actions needed to encourage certain subgroups, leads to a current underscreening in certain subgroups (e.g. women with lower socio-economic status).

To avoid opportunistic screening and overconsumption, the reimbursement of PAP smear tests is restricted to once every three years since 2013. Within the screening program, the PAP smear test and the related analyses are complimentary for the women, only the consultation with the GP or gynecologist is charged. This reimbursement of the consultation can vary depending if the physician is conventioned or not. Also the laboratory may charge additional costs (e.g. for administration, materials) and may perform HPV-tests outside the context of triage. The costs for this additional test are also directly charged to the patient. The prevention of cervical cancer is also included in the medical file (GMD+). The HPV test is currently performed for triage purposes and is only reimbursed after a second reading of a positive cytological test (ASC-US). The succession of HPV test after a cytological test requires an additional PAP smear test (and second consultation), if conventional cytology analysis is used. A second PAP smear test is not needed if liquid-based cytology analysis is used.

The clinicians are informed on the test results and are responsible to inform the screened woman and to organize the aftercare (secondary examinations and treatments). However, since the letter is directly send to the eligible women, the GPs are often unaware about the frequency of screening tests of their patients. This situation hampers the central role of the GP in sensitizing the woman about prevention of (cervical) cancer.

The organization of a uniform sensitization program of the eligible women is in progress, but currently different organizations and sensitizations programs still exist, which could increase the risk to disseminate different messages. An evidence-based, objective and comprehensible patient leaflet which contains the advantages and disadvantages of cervical cancer screening, could facilitate the informed decision making by the woman.

1.1.1.2 French-speaking region

Nevertheless a broad consensus (in 1992) on cervical cancer screening by the cancer detection centers of the French-speaking universities and professional scientific societies, no formal screening program has been set up yet.[2] In this consensus document, the uniform cytological interpretation and follow-up is similar to the European guidelines and the Flemish instructions. Only the definition of the target age groups differs: the PAP smear screening should begin 3 years after initiation of sexual contact (in contrast to the defined age groups in the Flemish region).

1.1.1.3 Brussels

Currently no formal screening program has been set up by the Brussels government. Also no agreement has been achieved between the Flemish and the Brussels government for the inclusion of the Flemish women living in Brussels in the Flemish cervical cancer screening program.

1.1.1.4 Discussion

The decentralization of preventive healthcare services has led to a variety of practices over the country. Whereas in the Flemish region a screening program has been set up and continuously evolving, in the other two regions of the country (French-speaking region and Brussels) no initiatives has been started. This means also that the women in these parts of the country only are tested by opportunistic screening and that no initiatives have been taken

to encourage subgroups of the population of eligible women to participate to the screenings modalities.

The screening program in the Flemish region is still a novel program, which mainly consists of a call-recall system. The quality aspects of the test procedure and analysis is under development. The lack of a centralized notification of test results, hampers a good communication with the patient. Currently the laboratory and/or physician himself needs to inform the patient and even the moment of announcement can vary between laboratories due to a variety in waiting period.

Despite the setup of a screening program, opportunistic screening is still common practice and is often linked to an overconsumption of PAP smear tests[3, 4].

The above-mentioned summary and analysis of the current screening program is based on a full report by the working group on cervical cancer screening[1]. Within the organisational framework of the screening program, already a working group is implemented to evaluate the content and the quality of the program, which in short and long term will benefit the functioning of the screening program.

The current screening program in the Flemish region is focused on the setup of a call-recall system, in which the woman is encouraged to make an appointment every 3 years with her GP or gynecologist for a PAP smear test. Only after a second positive reading of the cytological analysis, a reimbursement of a HPV test is foreseen. To facilitate the coordinating role of the GP, he/she should be informed about the screening status of his/her patients. No quality procedures have been elaborated to increase the inclusion of more vulnerable subgroups within the eligible population and no quality procedures have been developed for the test and analysis procedure. In the French-speaking region and in Brussels, no screening program has been set up and the women are only screened on own initiative.

The recognition of the strong causal relationship between persistent cervical infection with high-risk human papillomavirus (HPV) types and occurrence of cervical cancer[5] has led to the development of a series of HPV DNA or RNA tests.

Detection of high-risk (hr) HPV DNA is considered to be potentially useful as a primary screening test, solely or in combination with cervical cytology to detect cervical pre-cancer and to rule it out in the predominately healthy population. In addition new tests, based on the molecular carcinogenic pathways subsequent to expression of viral oncogenes, have been developed.

In this report, we have updated and extended previously conducted meta-analyses and systematic reviews which synthesize current knowledge on the evidence regarding HPV-based primary screening as a new paradigm of cervical cancer prevention and on the identification of HPV assays[6].

1.1.2 Methods

1.1.2.1 Literature Retrieval

A meta-analysis has been published by the Unit of Cancer Epidemiology in which an evaluation was made of the accuracy of HPV testing versus cytology in primary screening of cervical cancer[6]. To update this systematic review, the electronic database Medline was searched using the search string in Box 1. The search was limited to publications published after January 01, 2012.

Box 1 – Search string used to retrieve relevant literature in Medline

((Uterine Cervical Neoplasms [MeSH Terms] OR Uterine Cervical Dysplasia [MeSH Terms] OR Cervical Intraepithelial Neoplasia [MeSH Terms] OR ((cervix [tw] OR cervical [tw] OR cervico* [tw]) AND (cancer* [tw] OR carcinoma OR adenocarcinoma OR neoplas* [tw] OR dysplas* [tw] OR dyskaryos* [tw] OR squamous [tw] OR CIN [tw] OR CINII* [tw] OR CIN2* [tw] OR CINIII* [tw] OR CIN3* [tw] OR SIL [tw] OR HSIL [tw] OR H-SIL [tw] OR LSIL [tw] OR L-SIL [tw] OR ASCUS [tw] OR AS-CUS [tw])))

AND

(papillomaviridae [MeSH:NoExp] OR alphapapillomavirus [MeSH Terms] OR “DNA, viral” [MeSH Terms] OR Papillomavirus Infections [MeSH Terms] OR Tumor Virus Infections [MeSH Terms] OR “Cervix Uteri/virology” [MeSH Terms] OR HPV [tw] OR “human papillomavirus” [tw] OR papillomaviridae [tw] OR PCR OR “hybrid capture*” [tw] OR HC2 [tw] OR HCII [tw] OR “HC 2” [tw] OR “HC II” [tw] OR ((viral [tw] OR virolog* [tw]) AND (DNA [tw])))

AND

(Vaginal smears [MeSH Terms] OR Cytodiagnosis [MeSH Terms] OR Cell Transformation, Viral [MeSH Terms] OR Cytopathogenic Effect, Viral [MeSH Terms] OR ((pap [tw] OR papanicolaou [tw] OR vagina* [tw] OR cervical [tw] OR cervix [tw] OR cervico* [tw] OR cytolog* [tw]) AND (smear* OR test [tw] OR tests [tw] OR testing [tw] OR tested [tw] OR swab* OR scrap*))))

AND

(Screening [tw] OR screen* OR "Early Detection of Cancer"[Mesh])"

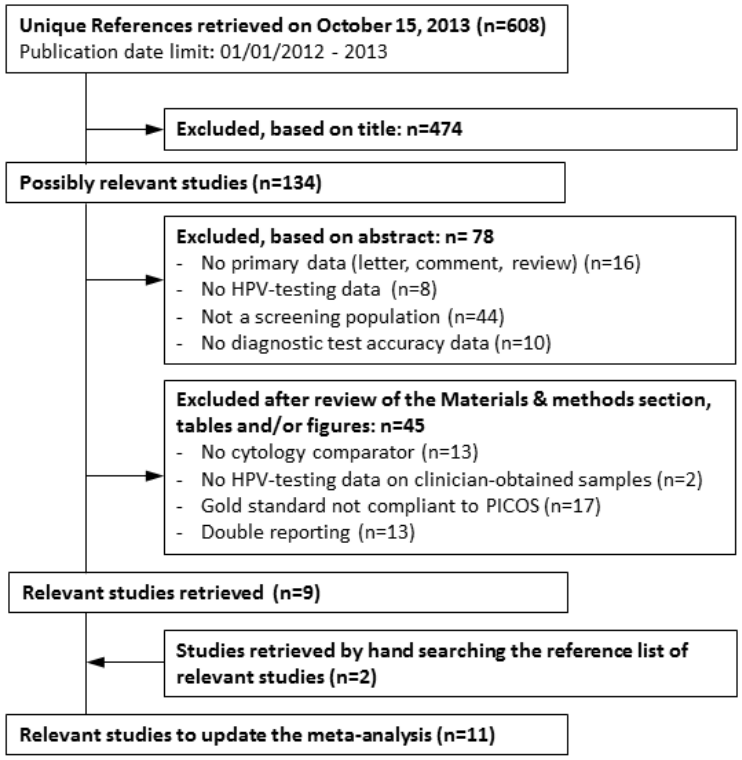
Criteria for inclusion of reports have been published elsewhere[7, 8]. Two types of study design were considered: (1) cross-sectional studies where women were submitted to concomitant testing with cervical cytology (conventional or liquid), a HPV DNA assay and, optionally, other screening tests and (2) randomised clinical trials where women were assigned to cytology, HPV testing or combined testing. In the assessment of absolute sensitivity and specificity, we distinguished three situations: (1) all cases were verified with a reference standard, (2) only screen test positive cases were verified and the assumption was made that none of the women being negative for all tests had underlying CIN2+ and (3) studies where also a random sample of women being negative for all tests were submitted to verification. For the evaluation of relative sensitivity, we considered the ratio of absolute sensitivities including intra-arm comparisons of randomised trials with combined cytology and HPV testing and the ratio of the detection rates of CIN2+ from the inter-arm comparison of RCTs. Studies were selected only when the participating women were representative of the general population.

1.1.3 Results

1.1.3.1 Literature Retrieval

A systematic review on the accuracy of HPV testing and cytology in primary cervical cancer screening had been published in 2012[6] by the Unit of Cancer Epidemiology. To update this systematic review and meta-analysis, a literature study was performed on studies published later than January 01, 2012. In total, more than 600 studies were retrieved and assessed for compliance to the PICOS. A 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) flow chart of the exclusion process is depicted in Figure 1. Additional to the studies included in Arbyn et al., 2012[6], 11 studies were found relevant and included in the analysis[9-19].

Figure 1 – Prisma flow chart summarizing the selection of relevant studies



1.1.3.2 Study Characteristics

A comprehensive summary of the study characteristics of the 11 studies are summarized in Table 1, Table 2, Table 3 and Table 4.

Table 1 – Study characteristics

Author	Year	Country	Location	Population	Inclusion criteria	Exclusion criteria	Study size	Age	Publication format
Girianelli	2006	Brazil	Duque de Caxias, Nova Iguacu	Women willing to participate in a screening study.	had already had sexual intercourse; between 25 and 59 years of age	Pap test ≤3y ; pregnancy ; Delivery ≤6m; hysterectomy	1775	Mean: 39 Range: 25-59	Published article
Szarewski	2007	UK	London	Women who were due for a routine screening smear and were either identified opportunistically (at the Margaret Pyke Centre) or from Prior Noticifation Lists (PNLs) of participating general practitioners.	Not documented	Previous ablative or excisional treatment	920	Median: 29 (opportun -istic) Median: 41 (PNL)	Published article
Leinonen	2012	Finland	South Finland	Women invited for cervical cancer screening.	Not documented	Not documented	HPV: 62143 Cyto: 70051		Published article
Longatto-Filho,	2012	Brazil and Argentina	Campinas (Brazil), São Paulo (Brazil), Porto Alegre (Brazil), and Buenos Aires (Argentina)	Consecutive women were invited to gynecological consultations and tests examination.	Not documented	Not documented	11955	Mean: 38	Published article
Rijkaart	2012	The Netherlan ds	Utrecht	Women invited for the regular cervical screening programme, and willing to participate in the study	Written informed consent	history of CIN2+; abnormal cytology ≤2y	25658	Median: 44 Range: 29-61	Published article

Author	Year	Country	Location	Population	Inclusion criteria	Exclusion criteria	Study size	Age	Publication format
Zhao	2012	China	Xiangyuang; Beijing; Henan	Women willing to participate in women in population-based cross-sectional cervical cancer screening studies.	Sexually active; intact uterus; provided written informed consent.	Pregnancy; a history of CIN2+ or pelvic radiation; screened ≤5y	2624	Range: 16-54	Published article
Cuzick	2013	UK	London	Residual material from samples of 6000 women who attended for routine screening.	Not documented	Unsatisfactory cytology sample	6000	Median: 37 Range: 20-66	Published article
Diamanto poulou	2013	Greece	Athens	Consecutive women presenting at outpatient clinic for routine screening, willing to participate.	Not documented	Recent labor	1317	Median: 34 Range: 18-65	Published article
Ferreccio	2013	Chile	Santiago	Women willing to participate in a screening trial.	Not documented	Pregnancy; hysterectomy; virginity.	8265	Range: 25-64	Published article
Ikenberg	2013	Europe	Belgium, France, Germany,Italy, and Spain	Women undergoing routine cytology-based cervical cancer screening at gynecologist practices and hospital-based screening centers	Not documented	Pregnancy; previous hysterectomy	25577	Mean: 40 Range: 18-74	Published article
Nieves	2013	Mexico	Michoacan	Women invited to participate in a screening study	Women accepting participation with complete screening results, informed consent.	Pregnancy; history of Pap smear screening or knowledge of their Pap results within the last 3 years; history of prior pelvic radiation	2049	Median: 39 Range: 30-50	Published article

Table 2 – Study Characteristics (continued)

Study	Period	Tests
Girianelli, 2006	December 2001- July 2002	LBC, cPAP, HC2
Szarewski, 2007	January 2001 - November 2004	cPAP, HC2
Leinonen, 2012	2003-2007	cPAP, HC2
Longatto-Filho, 2012	February 2002 - June 2003	LBC, HC2, VIA, VILI
Rijkaart, 2012	October 2003 - August 2005	cPAP, HC2
Zhao, 2012	1999 to 2007.	LBC, HC2, VIA
Cuzick, 2013	Not documented	LBC, HC2, BD, COBAS4800, Abbott, APTIMA, Pretect
Diamantopoulou, 2013	March 2006 – September 2008	LBC, CLART
Ferreccio, 2013	Not documented	cPAP, HC2, VIA
Ikenberg, 2013	Not documented	LBC or cPAP, p16/Ki-67 dual stain, HC2
Nieves, 2013	February 2009 - April 2009	LBC, HC2, APTIMA

Table 3 – Study Characteristics (continued)

Author	Year	Gold standard	Criteria for gold standard application	Masking of screeners	Correction sample	Categorization of gold standard application
Girianelli	2006	Colposcopy + targeted biopsy.	Women with at least one abnormal screen test. Cyto: ASCUS+ HPV: 1 RLU + an additional random sample of women with all negative tests	The samples (HPV self + clin, Cyto) were masked, and study numbers were randomly assigned.	Yes, random sample of women with all negative tests.	CIN2 CIN3 adenocarcinoma in situ, squamous carcinoma adenocarcinoma
Szarewski	2007	Colposcopy + targeted biopsy.	- Women with at least one abnormal screen test. Cyto: LSIL+	Staff in the cytology, histopathology and molecular biology laboratories were blinded to other results.	Yes, random sample of women with	CIN1+ CIN2+

			HPV: 1 RLU - a randomly selected 5% sample of women who tested negative on all three tests		all negative tests.	
Leinonen	2012	Colposcopy + targeted biopsy.	Cyto-arm: LSIL+:immediately referred ASCUS: rescreening after 12-24 months. HPVarm: hrHPV+/cyto-: re-screening after 12-24 months	Not documented.	No	CIN1 CIN2 CIN3 or AIS ICC
Longatto-Filho	2012	Colposcopy + targeted biopsy. If CIN2+: immediate treatment. If CIN1 or (hrHPV+ and no CIN) and/or abnormal Pap and/or hrHPV+: 3y follow-up.	Women with at least one abnormal screen test. HPV: 1 RLU Cyto: ASCUS+	Not documented	No	Normal CIN1 CIN2+
Rijkaart	2012	Colposcopy + targeted biopsy	- HrHPV+/BMD or BMD+:directly referred - hrHPV-/BMD: repeat cytology at 6 and 18m, and referred if cytology was abnormal (BMD+). Control subset: - <BMD/hrHPV+: cyto and HPV-test at 12m, referral if BMD+. combined cyto/HPV-testing at 24m, referral if at least one test+. - <BMD/hrHPV-: combined cyto/HPV-testing at 24m, referral if at least one test+.	Not documented	No	Normal CIN1 CIN2 CIN3 ICC

Zhao	2012	Colposcopy + targeted biopsy or 4 random biopsies.	1) VIA+: colposcopy and directed biopsy, ECC if necessary; 2) HC2+ or ASC-H and LSIL+ on LBC: colposcopy and four-quadrant biopsies, ECC if necessary.	Blinded histological review	No	Normal CIN1 CIN2 CIN3+
Cuzick	2013	All results are presented based on the local histopathology, and the highest grade of abnormality seen in the biopsy or treatment specimen was used.	A subset of women with abnormal cytology.	Not documented.	No	Normal Borderline CIN1 CIN2 CIN3/CGIN HG Invasive cancer
Diamantopoulou	2013	Colposcopy + targeted biopsy or random biopsies (n=3).	Women with at least one abnormal screen test. HPV: 1 RLU Cyto: ASCUS+	Not documented	No	Normal CIN1 CIN2 CIN3 SCC Adenocarcinoma
Ferreccio	2013	Colposcopy + targeted biopsy	Women who are hrHPV+ (1RLU) or have abnormal cytology (ASCUS+) and a subset (non-random) of screen-negative women.	Cytotechnologists and lab technicians were blinded to test results of HPV and cytology, respectively. Clinicians performing the colposcopy were blind to the screening status by study design; however some participants may have informed them of their screening results during the visit. Pathologists were blind to the HPV test result, but not	Yes	CIN2 CIN3 carcinoma

				necessarily to the Pap test result, since the laboratory procedure is to check any previous Pap tests at the time of histological analysis.		
Ikenberg	2013	Colposcopy + targeted biopsy. Cases where no biopsies were taken during the colposcopic examination were considered negative for disease.	Immediate colposcopy for subjects with abnormal Pap cytology results (ASC-US+), and/or a positive p16/Ki-67 dual-stained cytology result, and/or hrHPV+, unless HPV was the only positive test in women younger than 30 years.	cytotechnologists/pathologists were blinded to all study results. colposcopists were aware of Pap cytology and HPV test results but blinded to any dual-stained cytology results. All local histology results were verified by members of an independent quality control (QC) review board comprising a total of five pathologists, blinded to all study results.	Correction for incomplete verification	CIN2+ CIN3+
Nieves	2013	Colposcopy + colposcopy-directed cryotherapy or colposcopy-directed biopsy and/or multiple random biopsies.	Women with at least one positive screening test result Cytology: ASCUS+ HPV-test: no cut-off documented.	All HPV testing was performed by technicians who had no knowledge of, or access to, cytology results.	No correction.	CIN2+ CIN3+

Table 4 – Study Characteristics (continued)

Author, year	Study design	Remarks	Author contacted
Girianelli, 2006	Experimental cross-sectional study with concomitant cytology and HPV-testing (self-sample + clinician-sample).		No
Szarewski, 2007	Experimental cross-sectional study with concomitant cytology and HPV-testing (self-sample + clinician-sample).		No
Leinonen, 2012	RCT		No
Longatto-Filho, 2012	Experimental cross-sectional + prospective study with concomitant cytology, HPV-testing (self-sample + clinician-sample), VIA and VILI.		No
Rijkaart, 2012	Experimental cross-sectional study with concomitant cytology, HPV-testing		No
Zhao, 2012	Experimental cross-sectional study with concomitant cytology, HPV-testing (self-sample + clinician-sample).		Yes
Cuzick, 2013	Retrospective study. Cytology and histological verification. Afterwards HPV-testing on residual samples.	All results are presented based on the local histopathology and the highest grade of abnormality seen in the biopsy or treatment specimen was used. As the study was anonymised, the HPV result was not communicated to the women or the doctor and was not acted upon. This means that women who tested positive for HPV, but had normal cytology would not have been further investigated, and therefore disease ascertainment was not possible in this group. In addition, it was not possible to undertake histology review.	No
Diamantopoulou	Experimental cross-sectional study.		No
Ferreccio, 2013	Experimental cross-sectional study with concomitant cytology, HPV-testing.	Control group of screen- women that were verified is a convenience population with a higher risk of CIN2+. Verification bias adjusted estimates were calculated by using stratified sampling to weight up	No

		results from women who attended colposcopy, using the R Software CompareTests.13 The stratified sampling plan directly accounts for the fact that the screen-negative women referred to colposcopy were not a purely random sample, but were oversampled to have risk factors for cervical cancer, thereby adjusting the rate of missed cases to the actual risk profile of all the study participants.	
Ikenberg, 2013	Experimental cross-sectional study with concomitant cytology and HPV-testing.	Verification bias correction was performed to correct diagnostic accuracy estimates for disparities in colposcopy follow-up for the various test results, whereby for each test the combination disease rate was calculated and applied. Two-sided bias-corrected McNemar P values were determined with $P < 0.05$ considered statistically significant.	No
Nieves, 2013	Experimental cross-sectional study with concomitant cytology and HPV (self- and clinician samples).		Yes

1.1.3.3 Primary screening for cervical (pre-)cancer

The updated meta-analysis of the cross-sectional accuracy of HPV tests contains data from 60 studies, among which 9 randomised trials. In the large majority of studies, the HC2 or GP5+6+ PCR were used. The last couple of years data have been published on the performance of HPV-based screening with other HPV DNA or RNA detection systems (Cervista, Cobas-4800, HPVCare, Papillocheck, APTIMA, Pretect HPV Proofer and others)[20].

1.1.3.4 Absolute cross-sectional accuracy of HPV testing

Overall, the sensitivity of HC2 (at standard conditions: RLU≥1) for detecting underlying CIN2+ and CIN3+ was 91% (95% CI: 89-93%) and 95% (95% CI: 94-97%), respectively (Table 5, Figure 2, Figure 3). The heterogeneity in the sensitivity was very large in studies conducted in developing countries (probably due to the variability in the quality of colposcopy and histology verification)[7]. The inter-study variation was substantially reduced in studies conducted in industrialised countries and was even non-significant in Chinese studies, where an improved gold standard with multiple (random) biopsies was applied (Figure 2, Figure 3).

In European and North-American studies, the pooled sensitivity for CIN2+ was 96% (95% CI: 95-98%), whereas the pooled specificity was 91% (95% CI: 89-91%). The accuracy values of HC2 for CIN3+ were similar to those for CIN2+. Eleven percent (95% CI: 9-12%) of the screened population was hrHPV-positive.

The sensitivity of other HPV assays evaluated in primary screening was consistently high for detection of CIN3+ (in general >94%, except HPVCare=87%). The specificity of these other tests varied between 86% and 91%.

Table 5 – Meta-analyses on the test performance of HPV DNA testing in primary screening to detect CIN2+ or CIN3+

Test	Test cut-off	Outcome	Studies	Sensitivity		Specificity		Test-positivity rate
				Estimate (95% CI)	Range	Estimate (95% CI)	Range	Estimate (95% CI)
HC2	1 pg/ml	CIN2+	41	0.91 (0.89-0.93)	0.50-1.00	0.89 (0.87-0.90)	0.61-1.00	0.13 (0.12-0.14)
		CIN2+	18*	0.96 (0.95-0.98)	0.69-1.00	0.91 (0.89-0.92)	0.85-0.96	0.11 (0.09-0.12)
		CIN3+	26	0.95 (0.94-0.97)	0.62-1.00	0.89 (0.88-0.91)	0.82-0.95	0.12 (0.10-0.13)
		CIN3+	10*	0.98 (0.97-0.99)	0.94-1.00	0.91 (0.88-0.93)	0.85-0.95	0.10 (0.08-0.12)
GP5+/6+	+ signal	CIN2+	3	0.95 (0.94-0.97)	0.94-1.00	0.95 (0.93-0.96)	0.86-0.96	0.08 (0.05-0.10)
Cervista	+ signal	CIN3+	1	0.95 (0.92-0.99)	-	0.90 (0.90-0.91)	-	0.11 (0.10-0.12)
Abbott	+ signal	CIN3+	1	0.95 (0.85-1.00)	-	0.87 (0.86-0.88)	-	0.13 (0.13-0.14)
Aptima	+ signal	CIN3+	4	0.99 (0.94-1.00)	0.96-1.00	0.91 (0.90-0.93)	0.90-0.93	0.09 (0.08-0.11)
Cobas 4800	+ signal	CIN3+	2	0.95 (0.87-1.00)	0.92-1.00	0.88 (0.81-0.96)	0.84-0.92	0.12 (0.05-0.20)
careHPV	1 pg/ml	CIN3+	1	0.87 (0.73-1.00)	-	0.86 (0.85-0.88)	-	0.15 (0.13-0.16)
MALDI-TOF	+ signal	CIN3+	1	0.94 (0.91-0.98)	-	0.89 (0.89-0.90)	-	0.12 (0.11-0.13)

** Restricted to studies conducted in North-America or Europe.*

Figure 2 – Meta-analysis of the sensitivity of HC2 as a primary screening test to detect CIN2+ in developing countries, industrialised countries and China

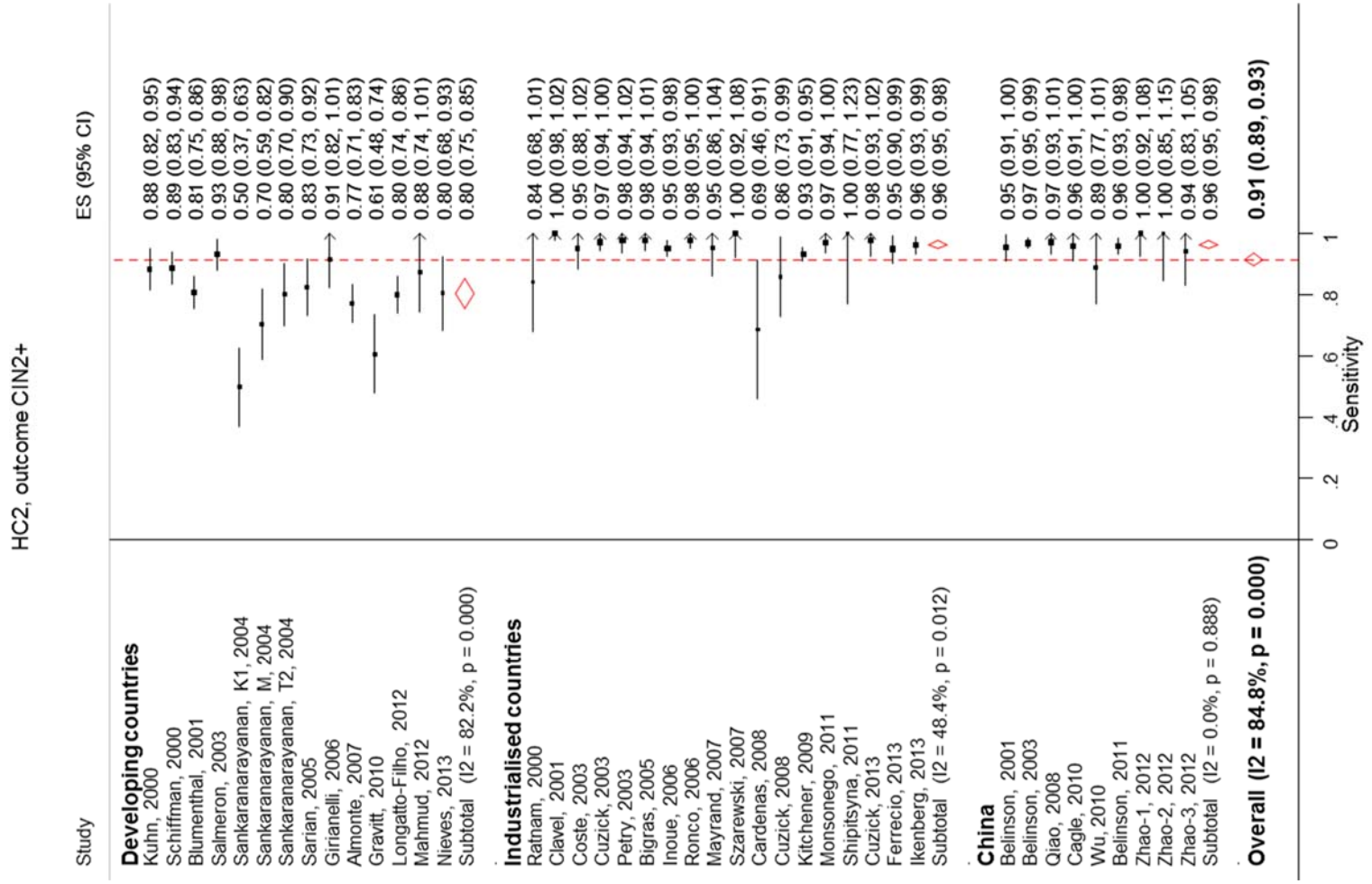
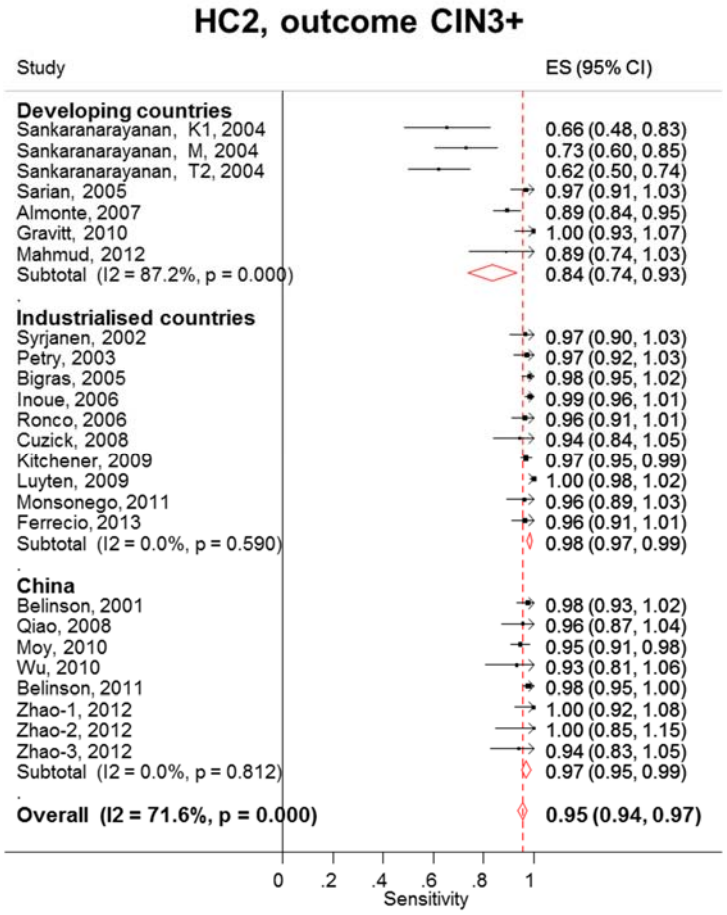


Figure 3 – Meta-analysis of the sensitivity of HC2 as a primary screening test to detect CIN2+ in developing countries, industrialised countries and China



1.1.4 Relative cross-sectional accuracy

Forrest plots for the meta-analyses of the relative accuracy of primary screening with HC2 compared to cytology are presented in Appendix I.

The sensitivity of HC2 (at standard cutoff=1pg/mL) was on average 24% to 40% higher than cytology, depending on the disease threshold (CIN2+ or CIN3+) or the cytological cutoff (ASC-US or LSIL) (Table 6). The specificity of HC2 for excluding CIN2+ was significantly lower than cytology: ratio of 0.98 (95% CI: 0.96-0.99) and 0.92 (95% CI: 0.90-0.94), considering the cutoffs ASCUS+ or LSIL+, respectively (Table 6).

The relative sensitivity and specificity of several HPV assays (GP5+/6+ PCR, HPVCare, Cobas 4800, Abbott RT PCR, PapilloCheck, Cervista, BD HPV, Pretect HPV Proofer, APTIMA) compared to HC2 is displayed in Table 7. For the majority of tests, the 95% CIs around the accuracy measures always included unity with the exception of APTIMA, which was on average more specific than HC2 (ratio=1.07; [95% CI: 1.05-1.08]). Another exception was Pretect HPV Proofer which was also more specific (ratio=1.12; [95% CI: 1.10-1.13], based on one study), but less sensitive than HC2 (ratio=0.74; [95% CI: 0.61-0.91]).

The combination of cytology with HC2 was, on average, 41% (95% CI: 36–47%) and 33% (95% CI: 29–37%) higher for the detection of CIN2+ or CIN3+, respectively, than cytology alone (at cut-off ASCUS+) (see Table 8). The specificity was 6% (95% CI: 6–7%) and 7% (95% CI: 7–8%) lower. In contrast, adding cytology to the HC2 increased the average sensitivity with only 7% (95% CI: 5–8%) for CIN2+ and 4% (95% CI: 3–6%) for CIN3+ compared to HC2 testing alone (Table 8). However, this resulted in a significant loss of specificity (ratios of 0.95; 95% CI: 0.94–0.96 and 0.94; 95% CI: 0.92–0.95, respectively).

Table 6 – Relative accuracy of virologic versus cytologic screening to detect CIN2+ or CIN3+

Comparison	Outcome	Relative sensitivity	Range	Relative specificity	Range	No. of studies
HC2 / Cytology (ASC-US+)	CIN2+	1.24 (1.17-1.32)	0.91-2.93	0.98 (0.96-0.99)	0.86-1.11	38/33
HC2 / conv. PAP (ASCUS+)	CIN2+	1.34 (1.20-1.50)	0.91-2.93	0.96 (0.95-0.98)	0.86-1.07	23/18
HC2 / LBC-ThinPrep (ASCUS+)	CIN2+	1.14 (1.07-1.21)	1.01-1.40	0.98 (0.96-1.01)	0.88-1.10	9
HC2 / LBC-SurePath (ASCUS+)	CIN2+	1.10 (0.97-1.25)	1.10-1.67	1.01 (0.97-1.06)	0.96-1.11	6
HC2 / Cytology (LSIL+)	CIN2+	1.38 (1.27-1.51)	0.89-2.73	0.92 (0.90-0.94)	0.67-1.03	26/23
HC2 / conv. PAP (LSIL+)	CIN2+	1.43 (1.28-1.60)	1.10-2.73	0.90 (0.87-0.94)	0.67-1.00	15/12
HC2 / LBC-ThinPrep (LSIL+)	CIN2+	1.25 (1.12-1.39)	0.89-1.78	0.92 (0.89-0.96)	0.86-0.98	6
HC2 / LBC-SurePath (LSIL+)	CIN2+	1.39 (1.13-1.72)	1.11-2.35	0.93 (0.90-0.97)	0.88-1.03	5
HC2 / Cytology (ASC-US+)	CIN3+	1.32 (1.15-1.51)	0.96-2.63	0.98 (0.97-1.00)	0.88-1.11	26/22
HC2 / conv. PAP (ASCUS+)	CIN3+	1.47 (1.19-1.81)	0.97-2.63	0.97 (0.95-1.00)	0.90-1.06	14/10
HC2 / LBC-ThinPrep (ASCUS+)	CIN3+	1.08 (1.01-1.17)	0.99-1.40	0.97 (0.93-1.00)	0.88-1.10	6
HC2 / LBC-SurePath (ASCUS+)	CIN3+	1.15 (0.96-1.36)	0.96-1.71	1.02 (0.97-1.07)	0.96-1.11	6
HC2 / Cytology (LSIL+)	CIN3+	1.40 (1.23-1.60)	0.97-2.52	0.93 (0.91-0.95)	0.84-1.03	18/15
HC2 / conv. PAP (LSIL+)	CIN3+	1.45 (1.21-1.74)	0.97-2.52	0.94 (0.90-0.98)	0.85-0.99	9/6
HC2 / LBC-ThinPrep (LSIL+)	CIN3+	1.27 (1.06-1.52)	1.00-1.53	0.90 (0.83-0.97)	0.84-0.95	4
HC2 / LBC-SurePath (LSIL+)	CIN3+	1.39 (1.03-1.88)	1.16-2.32	0.95 (0.90-0.99)	0.88-1.03	5

Table 7 – Relative accuracy of other HPV tests compared to HC2 (at RLU≥1) to find underlying CIN2+ or CIN3+ in primary screening

Comparison	Outcome	Relative sensitivity (95% CI)	Relative specificity (95% CI)	No. of studies
GP5+6+ / HC2	CIN2+	1.00 (0.96-1.04)	0.99 (0.91-1.07)	2
HPVcare / HC2	CIN2+	0.93 (0.85-1.01)	0.98 (0.96-1.01)	1
Cobas 4800 / HC2	CIN2+	1.00 (0.96-1.04)	0.99 (0.98-1.00)	3
Abbott / HC2	CIN2+	1.00 (0.96-1.03)	1.02 (1.01-1.03)	3
Papillocheck / HC2	CIN2+	0.99 (0.96-1.04)	0.99 (0.98-1.00)	1
BD HPV / HC2	CIN2+	1.00 (0.93-1.07)	0.99 (0.97-1.00)	1
Pretect HPV Proofer / HC2	CIN2+	0.74 (0.61-0.91)	1.12 (1.10-1.13)	1
APTIMA / HC2	CIN2+	0.98 (0.94-1.03)	1.04 (1.01-1.08)	5

Table 8 – Relative accuracy of combined testing with HC2 (at RLU≥1) and cytology (ASC-US+), compared to HC2 or cytology, to detect CIN2+ or CIN3+ in primary screening

Comparison	Outcome	Relative sensitivity (95% CI)	Relative specificity (95% CI)	No. of studies
HC2-CYTO(ASC-US+)/HC2	CIN2+	1.07 (1.05-1.08)	0.95 (0.94-0.96)	14/11
	CIN3+	1.04 (1.03-1.06)	0.94 (0.92-0.95)	10/7
HC2-CYTO(ASC-US+)/ CYTO(ASC-US+)	CIN2+	1.41 (1.36-1.47)	0.94 (0.93-0.94)	14
	CIN3+	1.33 (1.29-1.37)	0.93 (0.92-0.93)	10/9

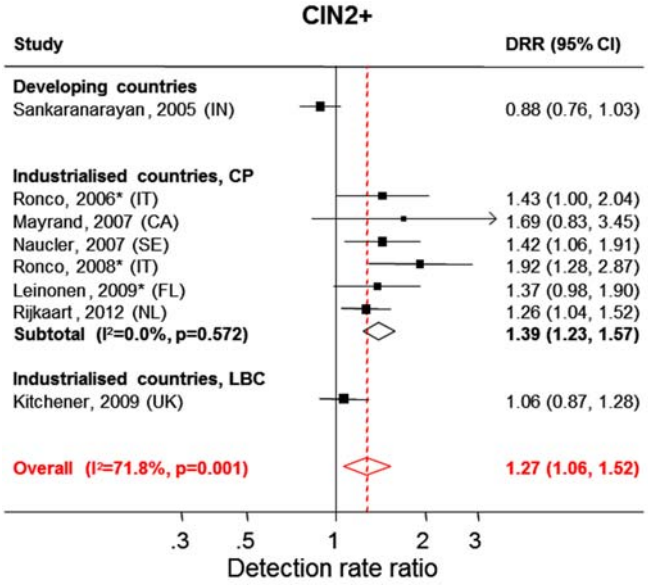
1.1.5 *Cross-sectional outcomes of randomised trials comparing cytology with HPV based screening*

No new studies could be identified than those included in a recent systematic review of the literature on three clinical applications of HPV testing, among which primary cervical cancer screening[6, 21].Therefore, we shortly summarize the main findings of the aforementioned review.

Figure 4 displays the relative detection rate (which is equivalent to the relative sensitivity) for CIN2+ of cytology applied in the control arm compared to hrHPV DNA testing in the experimental arm. hrHPV testing consistently showed higher detection rates in the trial conducted in industrialised countries where conventional cytology was applied in the control arms. In one trial, conducted in India, comparing screening with cytology, VIA (visual inspection after application of acetic acid), hrHPV testing with the HC2 assay and no screening[22], the relative detection rate (HC2 vs cytology) was lower than unity. These findings might be explained by a certain degree of gold-standard misclassification due to over-classifying non-high grade lesions which were HPV negative[23]. Evidence for these hypothesis was provided by observing a lower incidence of advanced cervical cancer and a lower mortality from cervical cancer in the HPV arm compared to the cytology arm[24]. Initial findings from the British trial, where LBC was used in the control arm, were interpreted as an indication that HC2 was not more sensitive than LBC[25] and that the consistent higher DR ration from the other RCTs conducted in Europe and North-America[26-30] were due to the use of conventional cytology in the control arm. Another explanation could that some over-diagnosis occurred in LBC interpretation in the British trial. Evidence for this latter explanation is provided by the lower incidence of CIN3+ in the UK trial (see deliverable 11.b. If the DR ratios which were not different from unity were not based on bias, no decreased CIN3+ should be observed in the subsequent screening rounds. Similar findings were observed in the detection rate ratios for the outcome CIN3+ (see Figure 5).

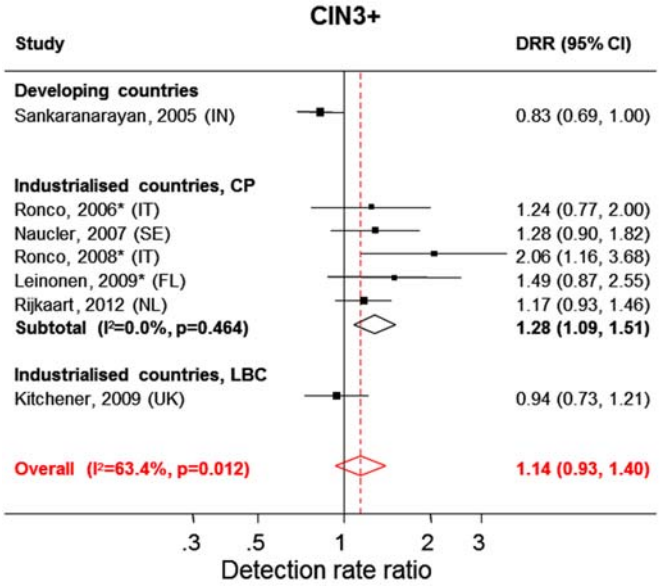
In all trials, with an experimental arm with combined screening, adding cytology to hrHPV testing yielded only a minor and statistically insignificant increase in sensitivity (pooled DR ratios of 1.06 [95% CI: 0.97-1.16] and 1.04 [0.92-1.17] for CIN2+ and CIN3+, respectively), see Figure 6.

Figure 4 – Meta-analysis of the detection rate ratio of CIN2+ in eight randomized trials identified by hrHPV testing versus cytology, studies are grouped by type of cytology (conventional cytology [CP] or liquid-based cytology [LBC]) and by industrialized versus developing countries



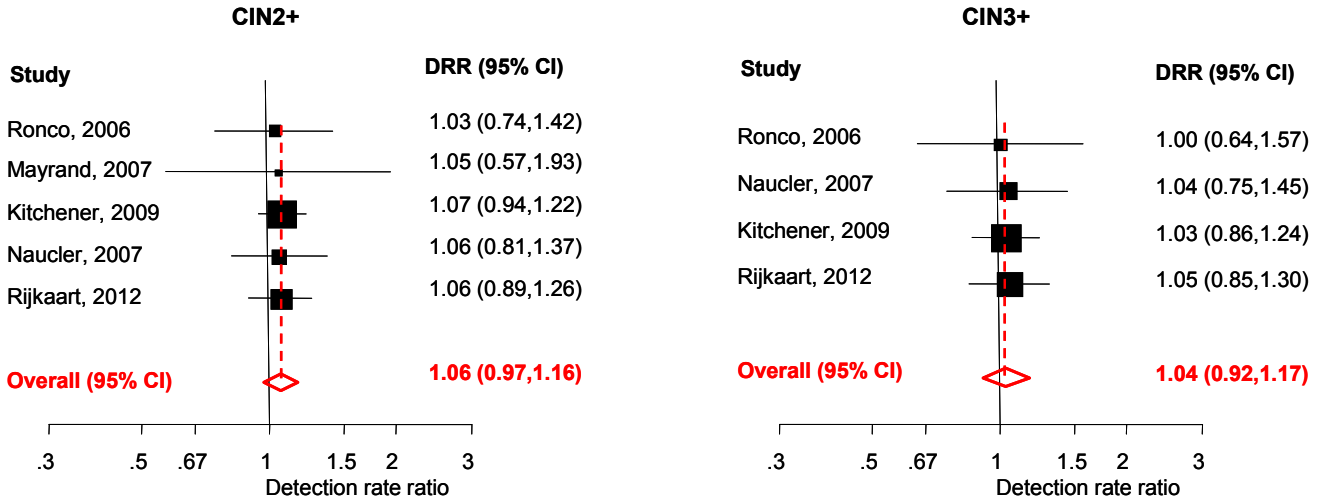
** Restricted to women older than 35 years.*

Figure 5 – Meta-analysis of the detection rate ratio of CIN2+ in eight randomized trials identified by hrHPV testing versus cytology, studies are grouped by type of cytology (conventional cytology [CP] or liquid-based cytology [LBC]) and by industrialized versus developing countries



** Restricted to women older than 35 years.*

Figure 6 – Relative sensitivity of HPV testing only vs. combined testing (HPV+cytology)



1.1.6 Discussion

The updated meta-analysis presented here confirms the conclusions that previously were published in the Vaccine journal (2012)[6].

The updated meta-analyses reinforces that hrHPV testing is substantially more sensitive than cytology in identifying underlying CIN2+ and CIN3+. However, one drawback is the lower specificity. A wide spread of accuracy estimates is observed in certain developing countries possibly explainable by variability in the reference standard. Further variation is observed according to the intensity of verification and methods to adjust for verification bias[7, 31].

However, it should be noted that the higher cross-sectional sensitivity of hrHPV testing for detecting CIN2+ and CIN3+ provides insufficient evidence that HPV-based screening will decrease the incidence of cervical cancer more than cytology-based screening. Most CIN2 and CIN3 lesions clear and it cannot be excluded from cross-sectional studies that HPV tests just pick up more regressive disease. For, this reason, hrHPV-based cervical cancer screening has not been recommended yet in the 2nd edition of the European Guidelines for Cervical Cancer Screening, considering evidence available in 2006[32].

Besides cytology, genotyping for HPV type 16 or 16 and 18, combinations of HPV16/18 genotyping and cytology, or HPV retesting to detect persistent infections can stratify the risk for CIN3+ and can be used in triage of hrHPV-positive women[33-36]. The 10-year cumulative risk associated with HPV16, HPV18 or other high-risk HPV infection, among women included in the Portland study was 17%, 14% and 3%, respectively[37]. In the Athena, trial, identification of HPV16 or HPV18 with the Cobas-4800 test showed similar sensitivity and PPV for CIN3+ (60% and 16%, respectively) as cytology at ASC-US+ cutoff (53% and 14%, respectively) to triage hrHPV positive women[38]. Other candidate markers which could be considered for triage are: testing for viral RNA of a limited number of types[39], p16INK4a immunocytochemistry or p16INK4a i67 double staining[40]. However, until present, evidence on the accuracy of these markers in triage of hrHPV positive women is still insufficient.

Currently, no marker or combination of markers allow perfect reflex triage. hrHPV positive women being cytology negative or HPV16/18 negative must be kept under surveillance and invited for repeat testing. Also HPV screening using a more specific test such as the APTIMA RNA assay[41] or Hybrid Capture-2 at a higher viral load cut-off[42] increases PPV with no or a small losses in cross-sectional sensitivity.

1.2 Efficacy and effectiveness of HPV vs cytology in primary screening for cervical cancer

1.2.1 Introduction

From the systematic review on the test accuracy of hrHPV testing in chapter 1.1, we have learnt that the sensitivity of hrHPV DNA testing is significantly and substantially more sensitive in detecting CIN2+ or CIN3+ than cervical cytology. However, these findings do not provide sufficient evidence for the thesis that introducing HPV-based screening will result in a lower incidence of cervical cancer. It is known that CIN2 and even CIN3 can regress spontaneously without treatment and from cross-sectional accuracy data, we cannot reject the hypothesis that mainly more non-progressive CIN2 or CIN3 are picked up by HPV testing which are missed by cytology[6]. To demonstrate that more progressive lesions are detected by HPV-based screening, we must demonstrate a lower incidence of cervical (pre-) cancer among women with a negative screening test. The highest level of evidence can be derived from RCTs. However, also cohort studies, in particular registry-based outcomes of screened cohorts, can contribute evidence by showing a lower incidence of CIN3+ or cancer after a negative HPV test compared to a negative cytology result[43]. In this review, we will summarize the longitudinal findings from randomized trials which compared cytology-with HPV-based screening.

In addition, we will address the question which HPV assays can be considered as clinically validated for use in primary screening for cervical cancer.

1.2.2 Clinical questions

1.2.2.1 Efficacy of HPV-based compared to cytology-based screening

What is the reduction of the cumulative incidence (detection rate) of CIN3+ and cervical cancer in women screened at enrolment with a hrHPV assay versus cytology and who were negative at enrolment screening?

PICOS components:

- P: women attending cervical cancer screening and screened with hrHPV DNA testing or with cytology or a combination of both screening tests and with negative screening test results at enrolment;
- I: screening with hrHPV DNA test, or with a combination of hrHPV DNA testing and cytology;
- C: screening with cytology;
- O: detection rate ratio of CIN3+ or cervical cancer observed in the 2nd screening round;
- S: RCTs with follow-up up to the 2nd screening round.

1.2.2.2 Low risk of cervical pre-cancer after a negative HPV test observed in screened cohorts

Clinical question: what is the cumulative risk of CIN3+ or cancer after a previous negative HPV test compared to after a negative Pap test?

- P: women attending cervical cancer screening and screened with hrHPV DNA testing or with cytology or a combination of both screening tests and with negative screening tests at enrolment;
- I: screening with hrHPV DNA test, or with a combination of hrHPV DNA testing and cytology;
- C: screening with cytology;
- O: cumulative risk after a previous negative Pap test versus after a negative hrHPV test;
- S: cohort studies including registry links between initial screening and outcome after five years or longer.

1.2.2.3 *Clinically validated HPV assays*

Clinical question: which HPV tests fulfil the equivalency criteria defined by Meijer et al.[44] regarding essay usable for primary cervical cancer screening?

Randomised trials have demonstrated that HPV-based screening using the HC2 assay or the GP5+/6+ PCR with EIA identification of 14 high-risk HPV types, is more effective in reducing the incidence of cervical cancer than cytology-based screening and therefore these assays should be considered as clinically validated[6, 21]. Experts have defined cross-sectional equivalency criteria allowing claims for other HPV DNA assays for use in primary screening[44].

The candidate test should demonstrate non-inferior sensitivity and specificity compared to HC2 or GP5+/6+ PCR, with lower 95% confidence interval bounds of ≥0.90 and ≥0.98, respectively. A representative set of samples (minimally 60 CIN2+ cases, 800 ≤CIN1 cases) derived from a population-based screening cohort should be selected[44]. Moreover, a high reproducibility (lower confidence bound ≥ 87%) should be reached.

A systematic search of published peer-reviewed references was performed using MEDLINE and Embase, completed with citations of the Meijer guideline, using www.scopus.com.

1.2.3 *Results*

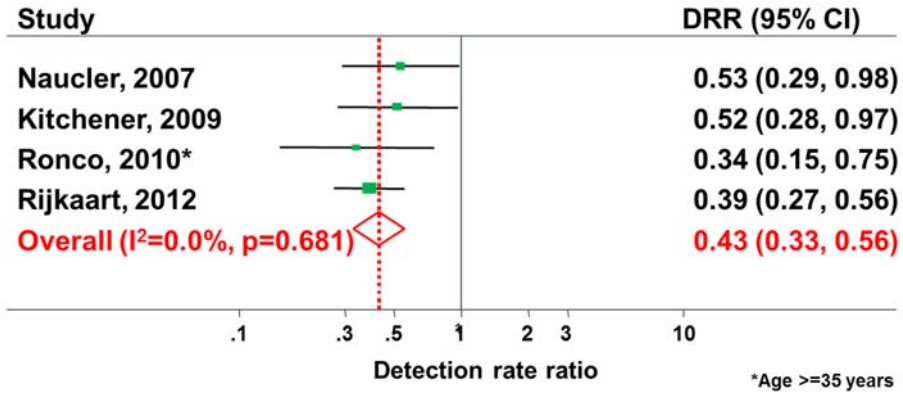
1.2.3.1 *Efficacy of HPV-based compared to cytology-based screening*

No new longitudinal results (second screening round) from other randomized trials could be identified besides the reports of four randomized trials conducted in Europe, respectively in Sweden, England, Italy and the Netherlands[25, 28, 29, 45], which were already included in a previous review prepared by the Unit of Cancer Epidemiology (Arbyn, Vaccine, 2012)[6]. No longitudinal outcomes, observed in subsequent rounds, were reported up hereto from the randomized trials conducted in Finland[11, 30, 46] or Canada (FOVAL trial)[47]. Another Canadian trial was excluded from our review since the criterion for the comparison groups was not fulfilled: randomization was based on the order of testing (collection for cytology or HPV as first or second test on the same individual)[27]. Moreover, no outcomes observed over subsequent screening rounds were foreseen[27].

Figure 7 shows the detection rate ratio of CIN3 or worse lesions detected in the second screening round among women who were HPV negative (in the HPV arm), over those who were cytology negative (in the control arm). A very consistent reduction in the detection of CIN3+ is observed in all four trials (p for heterogeneity: 0.681).

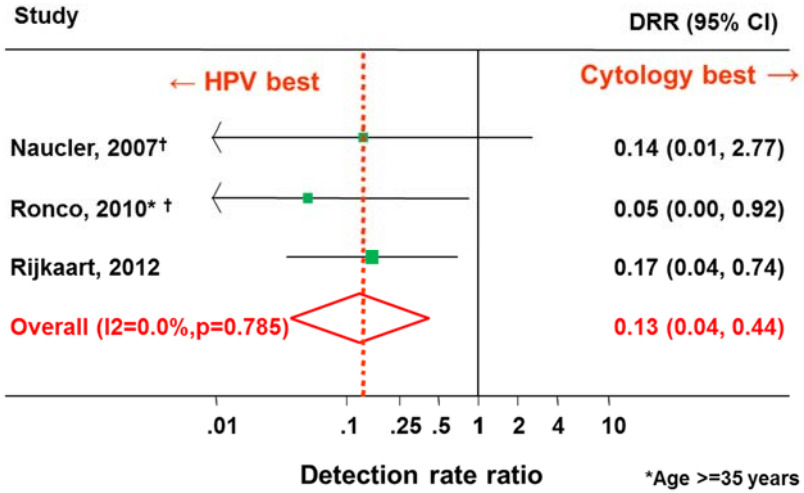
Figure 8 shows the same statistic but now for invasive cervical cancer for the three trials that provided published data. Although trials were designed to demonstrate a reduction in CIN3+, the pooled detection rate ratio as well as the ratios observed in two individual trials were significantly lower than unity.

Figure 7 – Meta-analysis of the main outcomes from randomised trials comparing HPV- and cytology-based cervical cancer screening. Relative detection rate of CIN3+, observed in the second screening round among women who were HPV-negative versus cytology-negative at enrolment



** Restricted to women of 35 years or older. Source: Arbyn, Vaccine 2012[6].*

Figure 8 – Meta-analysis of the main outcomes from randomised trials comparing HPV- and cytology-based cervical cancer screening. Relative detection rate of invasive cervical cancer, observed in the second screening round among women who were HPV-negative versus cytology-negative at enrolment

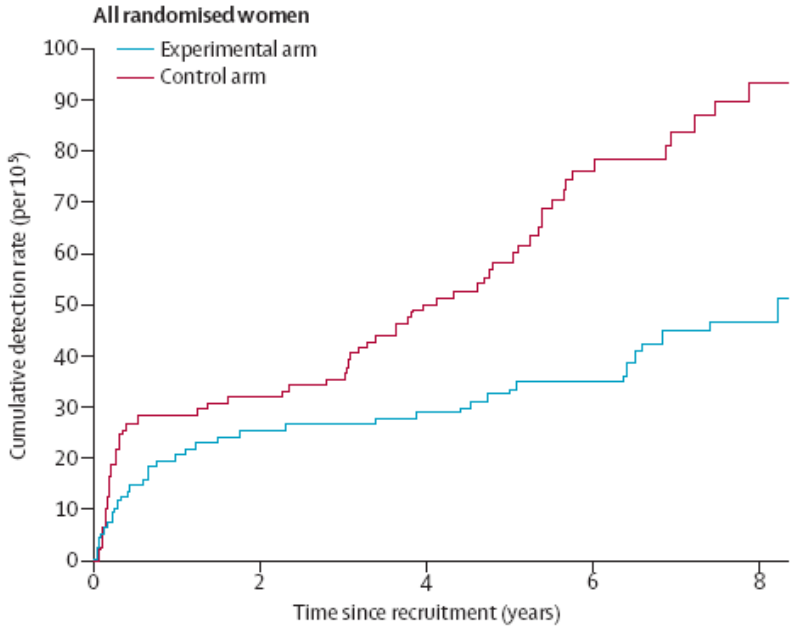


** Restricted to women of 35 years or older; † continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women). Source: Arbyn, Vaccine 2012[6].*

In addition, very recently, a pooled analysis of the individual data was performed, from the four mentioned trials was published[48]. This pooled analysis provided more details regarding the protection against invasive cervical cancer by HPV-based compared to cytology-based screening, such as:

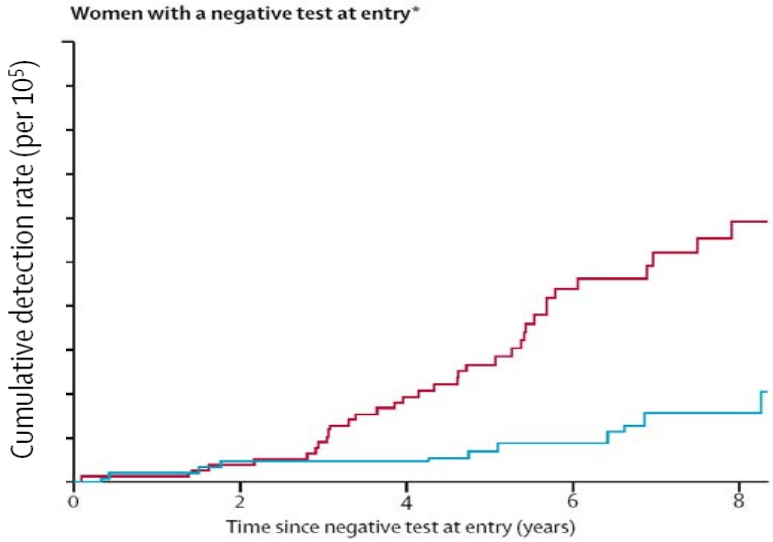
- the protective effect was observed only 2.5 years after screening (relative protection of 0.45; 95% CI: 0.25–0.81 versus 0.79, 95% CI: 0.46–1.36) before 2.5 years), but increased with follow-up time;
- the protective effect was similar for early (stage 1A) or advanced (stages ≥ 1A) cervical cancer;
- the protective effect was observed both in the total screened group (relative protection of 0.60; 95% CI: 0.40–0.89; see Figure 9) and in women with a negative screening test at base-line (relative protection of 0.30; 95% CI: 0.15–0.60; see Figure 10);
- there was no protective effect observed in the age group of <30 years (relative protection of 0.98 (95% CI: 0.19–5.20) (see 3 Target age group for cytological or virological screening for cervical cancer);
- HPV-based screening protects more against adenocarcinoma (relative protection of 0.31, 95% CI: 0.14–0.69) than against squamous cancer (relative protection of 0.78, 95% CI: 0.49–1.25).

Figure 9 – Cumulative detection rate of invasive cervical cancer among women included in the experimental arm (blue curve) screened with a hrHPV DNA test versus those included in the control arm (red curve) screened with cytology



Source: Ronco, Lancet 2013[48].

Figure 10 – Cumulative detection rate of invasive cervical cancer after a negative hrHPV DNA test (blue curve) compared to after a negative Pap test (red curve)



Source: Ronco, Lancet 2013[48].

1.2.3.2 Low risk of cervical pre-cancer after a negative HPV test observed in screened cohorts

The results from randomized trials among women are corroborated by observations from screened cohorts, indicating a prolonged duration of low risk of CIN3+ and of invasive cervical cancer after a negative hrHPV DNA test compared to after a negative cytology result.

1.2.3.3 Clinically validated HPV assays

Data regarding four hrHPV DNA tests and one hrHPV RNA assay[49] were retrieved, where the clinical performance for detecting high-grade CIN was assessed according to the Meijer guideline. The characteristics of the tests are summarised in Table 9. The outcomes of the validation assessment regarding non-inferiority with respect to sensitivity and specificity for CIN2+ and reproducibility, are summarised in Table 10 and Table 11, respectively.

Table 9 – Characteristics of HPV assays, which are clinically validated for use in primary cervical cancer screening

Assay	Manufacturer	Control for DNA quality of the specimen
Hybrid Capture-2 (A signal amplification method targeting 14 hrHPV types)	Qiagen Corporation, Gaithersburg, MD, USA	No
GP5+6+PCR (PCR amplification of L1 region of HPV using the consensus primers GP5+/6+ primers, followed by identification by EIA)	Diassay, Rijswijk, The Netherlands	Yes
Abbott RT PCR hrHPV (Multiplex real-time PCR test that targets the (GP5+/6+) L1 region of 14 hrHPV types PCR)	Abbott Molecular, Inc., Des Plaines, IL, USA	Yes
COBAS-4800 (test amplifies the L1 gene of 14high-risk types using PGMY09/11 primers)	Roche Molecular Systems Inc., Alameda, CA, USA	Yes
PapilloCheck (PCR assay detecting a fragment of the E1 gene of 24 different HPV-types.: 6,11, 16, 18, 31, 33, 35, 39, 40, 42, 43, 44/55, 45, 51, 52, 53,56, 58, 59, 66, 68, 70, 73, and 82)	Greiner BioOne, Germany	Yes
qPCR(E6/E7) [1]: cutoff at RLU>1 (quantitative real time multiplex PCR targeting E6 or E7 genes high-risk HPV types and certain low-risk HPV types)	In house test	Yes
APTIMA (A multiplex NASBA amplification test targeting E6/E7 mRNA from 14 hrHPV types)	Gen-Probe Inc., San Diego, CA, USA, taken over by Hologic, Madison, WI, USA	Yes

Table 10 – Sensitivity and specificity of hrHPV assays and non-inferiority compared to the HC2 or GP5+/6+ PCR for detection of CIN2+

Evaluated assay	Study	Absolute sensitivity	Absolute specificity	Reference assay	Non inferiority test	
					p_sens	p_spec
Abbott RT	Carozzi, 2011	96.4%	92.3%	HC2	0.004	0.009
hrHPV test	Poljak, 2011	100.0%	93.3%	HC2	0.011	0.000
	Hesselink, 2013	95.6%	92.0%	GP5+/6+ PCR	0.028	0.000
Cobas-4800	Heideman, 2011	90.0%	94.6%	HC2	0.022	0.001
	Lloveras, 2013	98.3%	86.2%	HC2	0.009	0.001
Papillocheck	Hesselink, 2010	95.8%	96.7%	GP5+/6+ PCR	0.004	0.007
qPCR(E6/E7)	Depuydt, 2012	93.6%	95.6%	HC2	0.000	0.000
APTIMA	Heideman, 2013	95.5%	94.5%	GP5+/6+ PCR	0.067	0.000

Table 11 – Intra- and inter-laboratory reproducibility of hrHPV assays

Evaluated assay	Study	Intra-laboratory reproducibility		Inter-laboratory reproducibility	
		Value	LCIB	Value	LCIB
Abbott RT	Carozzi, 2011	98.5%	97.3%	-	-
hrHPV test	Poljak, 2011	100.0%	99.5%	100.0%	99.5%
	Hesselink, 2013	99.8%	99.1%	98.4%	97.2%
Cobas-4800	Heideman, 2011	98.3%	97.2%	94.6%	92.8%
	Lloveras, 2013	98.3%	97.2%	98.4%	97.2%
EPapillocheck	NVVP*	97.6%	96.3%	94.0%	92.1%
qPCR(E6/E7)	Depuydt, 2012	98.7%	97.8%	-	-
APTIMA	Heideman, 2013	96.0%	94.4%	95.1%	93.3%

Four hrHPV DNA tests (Cobas-4800, Abott RT PCR, Papillocheck, and a qPCR targeting E6/7 genes of hrHPV types) have been evaluated clinically. All fulfilled minimal requirements regarding relative sensitivity or specificity compared to HC2 or GP5+/6+ PCR. The reproducibility of all tests largely exceeded the required cut-off. Also the APTIMA assay matched the equivalence criteria, but this test detects mRNA for the viral E6/E7 genes and therefore longitudinal performance (low-risk continuing over a number of years after a negative APTIMA result) should be demonstrated.

As indicated in chapter 1.1, several other hrHPV DNA tests may be sufficiently accurate but are not yet validated using the criteria of Meijer et al.[44] Besides accuracy, also other characteristics will have to be taken in account in future choices of tests, such as high-through put capacity, costs, applicability on samples taken by the woman and the possibility to perform ancillary triage tests.

1.2.3.4 Conclusions

There is strong evidence that HPV-based screening results in a lower incidence of cervical cancer.

Besides the two assays evaluated in randomized trials (HC2 and GP5+6+ PCR), four other hrHPV DNA tests can be considered as clinically validated for use in cervical cancer screening (Abbott RT PCR, COBAS-4800, Papillo-Check, q E6-E7 PCR) since they fulfil the cross-sectional equivalency criteria for clinical validation. The APTIMA assay, detecting mRNA of the viral E6/E7 genes also fulfils these criteria, but more longitudinal data are needed, to demonstrate safety over five or more years after a negative test.

2 SCREENING INTERVAL FOR CYTOLOGICAL OR VIROLOGICAL SCREENING FOR CERVICAL CANCER

2.1 Screening intervals proposed in current guidelines for cytological screening

The screening interval for organised cytology-based cervical cancer screening recommended in EU recommendations is three to five years[32, 50]. Screening every five years is the national policy in the Netherlands and Finland, whereas it is also the policy for women older than 50 in Denmark, Sweden and England or older than 45 in Ireland. Screening every three years is recommended over the whole target age group in Belgium, France, Hungary, Italy, Lithuania and Spain and in younger women, in Denmark, Ireland, Sweden and England. Screening every year still is proposed in several countries such as Austria, Germany, Greece, Luxembourg, Slovakia, and in several other countries where opportunistic screening remains the mainstay[51, 52].

A key issue in the adherence to the recommended European, national or regional guidelines is the reimbursement policy. In Belgium, for instance, adaptation of the EU policy (screening every three years) in Flemish guidelines was hardly followed, since the reimbursement was not conditioned by the respect of the recommended screening interval[4]. However, the adoption of a new rule of reimbursement (restricted to one cytological screening examination once every two years) resulted in a 41% reduction in the total annual volume of examined Pap smears[53]. It is expected that further restriction of reimbursement (once every three years) will further reduce the amount of over-screening.

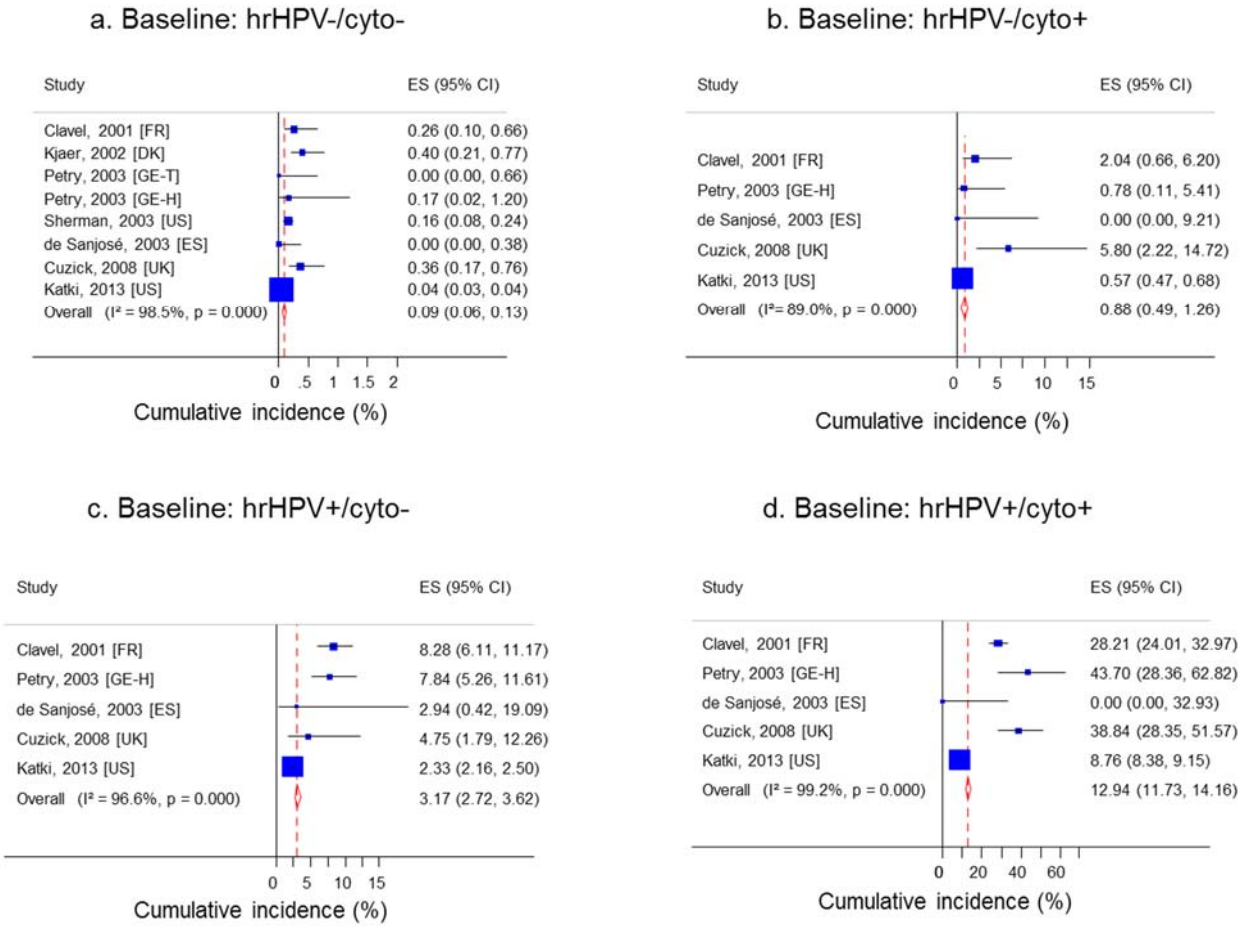
2.2 Low risk of cervical pre-cancer and cancer after a negative hrHPV DNA test observed in screened cohorts

The screening interval should be defined taking into account the cumulative risk of significant disease after a previous negative screening test. Other elements that should be considered are: the attendance at future screening, available resources and the burden of other health problems.

Figure 11 shows the cumulative risk to develop CIN3+ in the next five years according to the initial combined HPV and cytology status (pooled from 5 European[54-59] and two American screening cohorts)[60, 61]. The risk is very low for HPV-negative women (0.2% and 1.2%, for women without or with cytological abnormalities, respectively). However, for women who were hrHPV positive, this risk was substantially higher: 6% or 12%, for women without or with ASC-US or worse cytology at baseline, respectively. Follow-up of the European cohorts shows that the low risk of CIN3+ associated with a negative HPV test extends for at least six years (see Figure 12)[54]. The Portland study also provided outcomes regarding the risk of developing CIN3+ over 10 years in a population screened by cytology only where hrHPV testing was performed at baseline: 10.2% (if ASC-US+), 6.9% (if hrHPV+), 6.8% (if hrHPV+ or ASC-US+), 1.4% (if cyto-negative), 0.9% (if hrHPV-negative) and 0.8% (if negative for both cytology and hrHPV)[61]. More recently, follow-up outcomes over a period of 18 years were published, confirming the low risk of CIN3+ up to 18 years after a negative hrHPV DNA result (0.79%; 95% CI: 0.63% to 0.98%)[62].

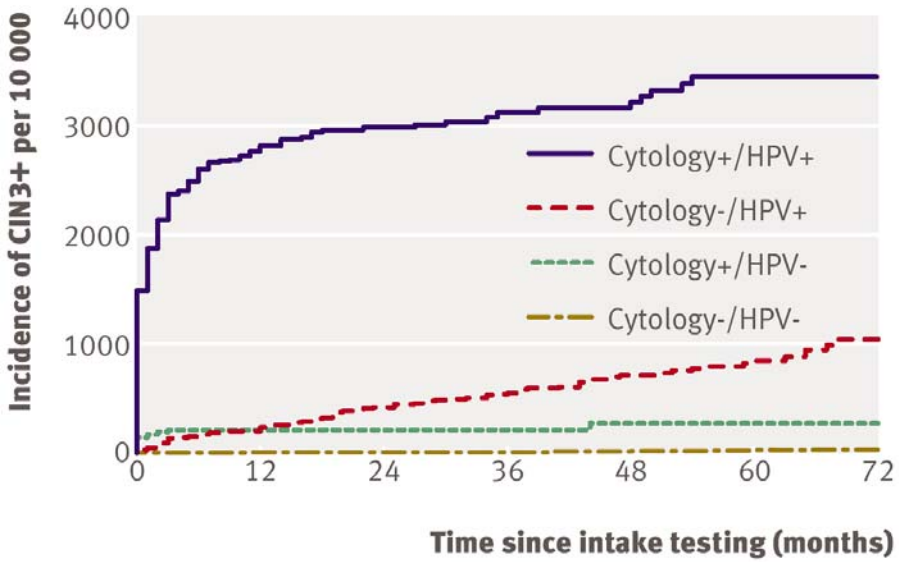
In the Kaiser-Permanente cohort, where women of 30 years or older were screened by cytology and HC2, the 5 year cumulative incidence of invasive cervical cancer was: 0.90% if positive for both hrHPV and cytology, 0.54% if hrHPV positive and cytology-negative, 0.16% if hrHPV-negative and cytology positive and 0.016% if negative for both (Figure 13)[63]. The 5-year cervical cancer risk corresponding with a negative hrHPV DNA result was 0.19% indicating that negative cytology does not stratify more the low-risk associated with one negative HPV test (Figure 14).

Figure 11 – Five-year cumulative incidence of CIN3+ among women attending cervical cancer screening who are at baseline cyto-negative/hrHPV-negative (a), cyto-positive/hrHPV-negative (b), cyto-negative/hrHPV-positive (c) and cyto-positive/hrHPV-positive (d). Pooled from 6 European and 2 American screening cohorts



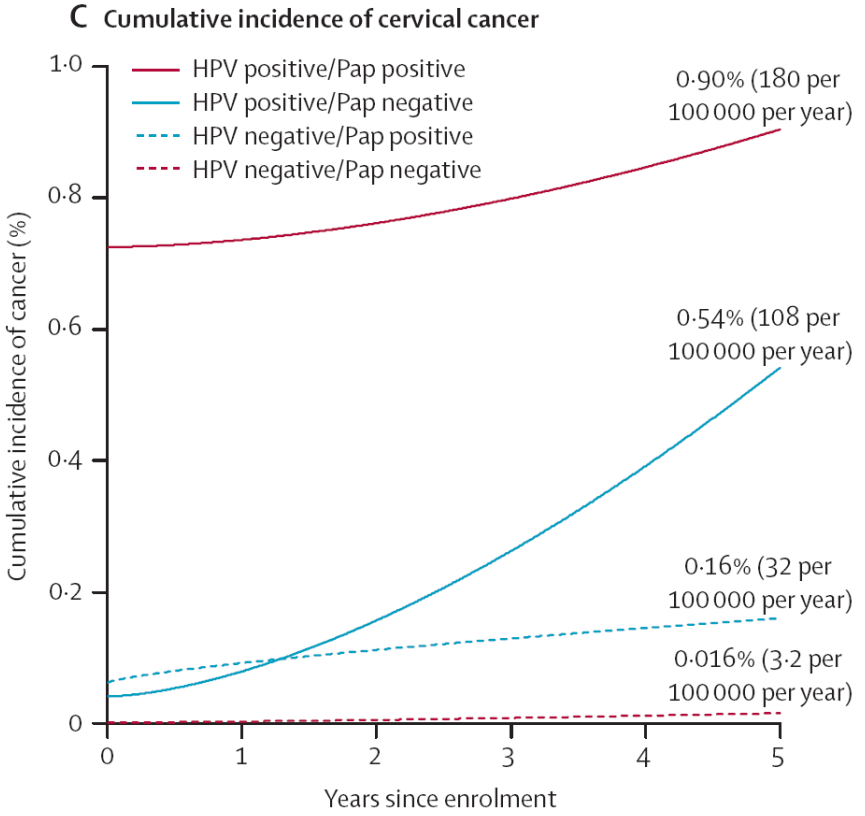
** The Portland study reported cumulative incidences over ~4 years[61]. Updated from Arbyn, Vaccine 2012[6].*

Figure 12 – Cumulative incidence of CIN3 or cervical cancer in five European cohorts screened at baseline with cytology and hrHPV DNA testing, according to the joint cytology/HPV test results at enrolment



Source: Dillner et al, BMJ 2008[54].

Figure 13 – Cumulative incidence of cervical cancer according the joint HPV/cytology status at baseline

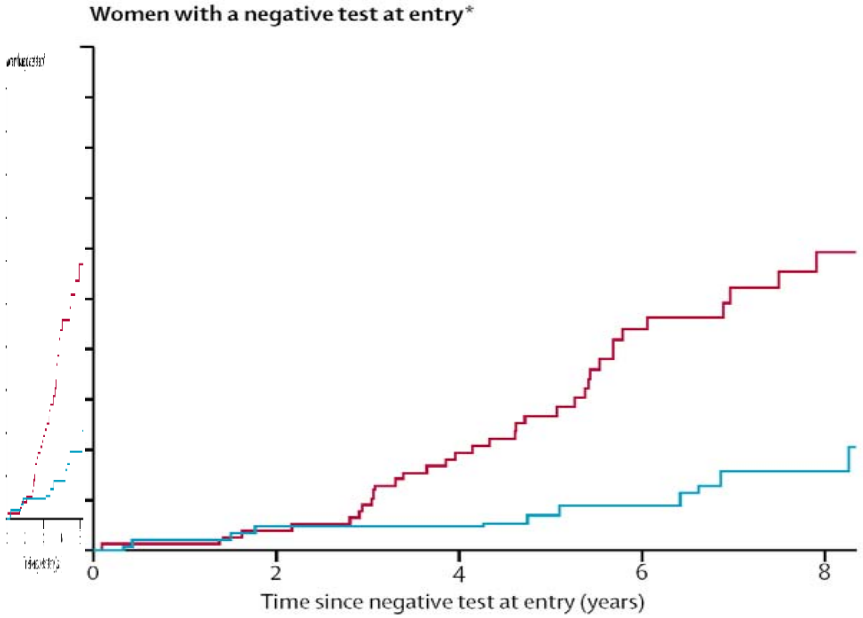


Source: Katki, Lancet Oncol 2011[63].

2.3 Increased protection against cervical cancer demonstrated in randomised trials

A recent pooled analysis of the individual data of four European randomised trials comparing cytology- with HPV-based screening showed a significantly lower risk after a negative hrHPV DNA test compared to a after negative cytology result[48]. The lower detection rate was only observable after two and a halve years and remained observable up to eight years.

Figure 14 – Cumulative detection rate of invasive cervical cancer after a negative hrHPV DNA test (blue curve) compared to after a negative Pap test



Source: Ronco, Lancet 2013[48].

2.4 Conclusion

The risk of CIN3+ or invasive cervical cancer after a negative hrHPV DNA test is significantly lower than after a negative Pap smear. This means that screening intervals can be extended safely up to five to ten years.

For reasons of safety and acceptability, the screening interval after a negative hrHPV test could be first defined at five years and extended further when the screening programme confirms the low longitudinal risk.

A negative co-test (negative cytology and negative HPV test) shows only marginally smaller risk than a negative HPV test alone. Therefore contesting does not offer additional safety allowing for even longer intervals than after a sole negative HPV test.

3 TARGET AGE GROUP FOR CYTOLOGICAL OR VIROLOGICAL SCREENING FOR CERVICAL CANCER

3.1 Target age group proposed in current guidelines for cytological screening

European guidelines propose starting screening in the age range 20–30, but preferentially not before age 25 years. Screening should be continued until the age of 60 or 65 years depending on the burden of disease and available resources[32, 50, 64]. Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous recent cytological results showing NILM[a]. It is recommended to continue screening at 3- to 5-year intervals until the age of 60 or 65[32, 50]. Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous (recent) normal cytology results.

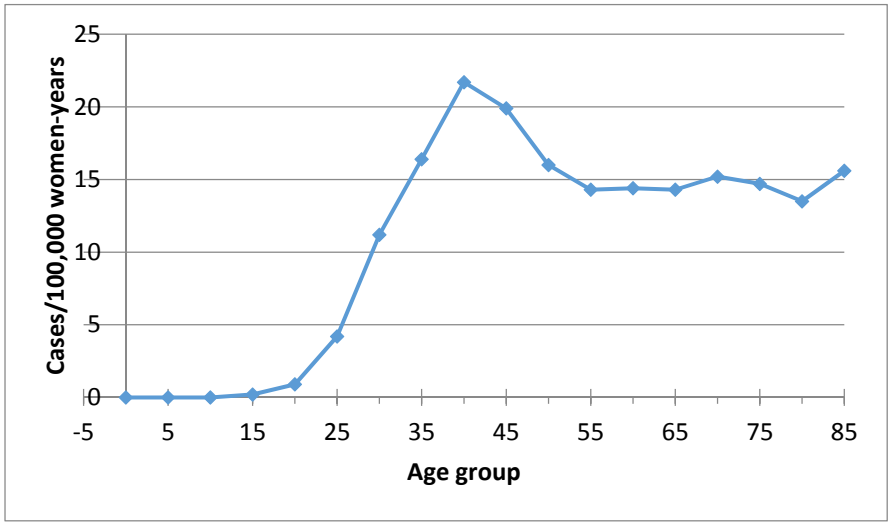
In Belgium, women are advised to have a Pap smear taken once every three years in the age group 25-64 (Table 12)[2].

It is recommended to start screening a few years before the age where the incidence of cervical cancer starts to rise[66]. The age-specific incidence of cervical cancer in Belgium is shown in Figure 15. An additional condition is that efficacy or effectiveness of screening at that age group is demonstrated. A recent large case-control study conducted in the UK, has demonstrated that cytological screening at age <25 was not effective (odds ratio not < 1) (see Figure 16 and Table 13)[67].

The incidence of invasive cervical cancer in Belgium starts rising in the age groups 25-34.

It seems that start age defined in the screening policy is justified.

Figure 15 – Age-specific incidence of cervical cancer in Belgium (average for the years 2008-10)



Source: Belgian Cancer Registry.

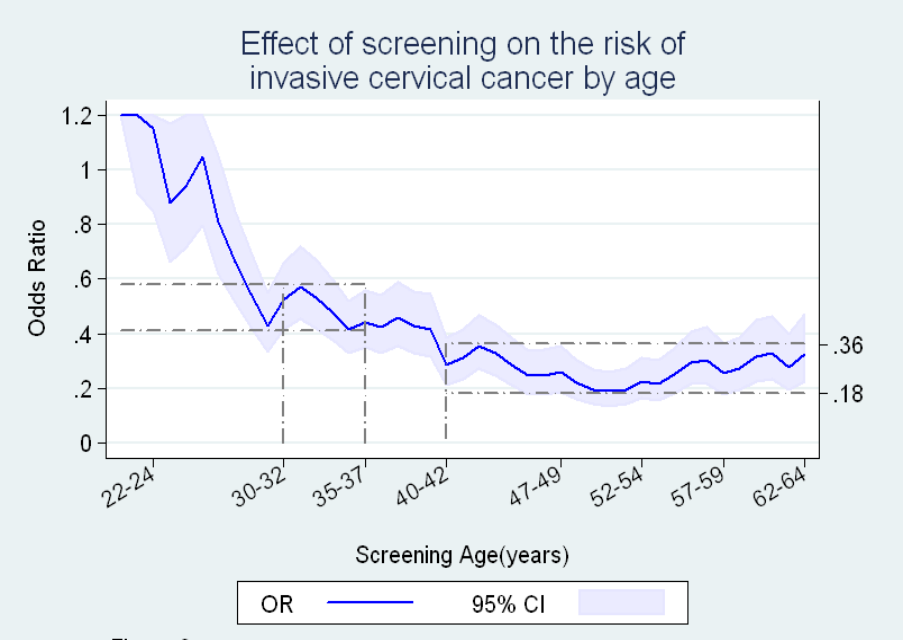
[a] NILM: negative for intra-epithelial lesion or neoplasia[65].

Table 12 – Policies for cervical cancer defined in the Member States of the European Union

	Target age group (years)		Screening
	Start	End	interval
Old member states (EU15)			
Austria	18	-	1
Belgium	25	64	3
Denmark	23	59	3 (<50)/5
Finland	(25) 30	60 (65)	5
France	(20) 25	(60) 65	3
Germany	20	-	1
Greece	20	-	1
Ireland	25	60	3 (<45)/5
Italy	25	64	3
Luxemburg	15	-	1
The Netherlands	30	60	5
Portugal	25	64	3
Spain	18-35	59-65	3/5
Sweden	23	60	3 (<50)/5
UK	(20) 25	(60) 64	3 (<50)/5
New Member States (EU12)			
Bulgaria	31	65	2
Cyprus	-	-	1
Czech Republic	25	69	1
Estonia	30	59	5
Hungary	25	64	3
Latvia	20	70	3
Lithuania	30	60	3
Malta	-	-	-
Poland	25	59	3
Romania	25	65	5
Slovakia	18	-	1
Slovenia	20	64	3

Adopted from Anttila et al., 2009[51, b].

Figure 16 – Protective effect (odds ratio) associated with cytological screening by age[67]



b Updated in the framework of the EUROCHIP-3 Network[68].

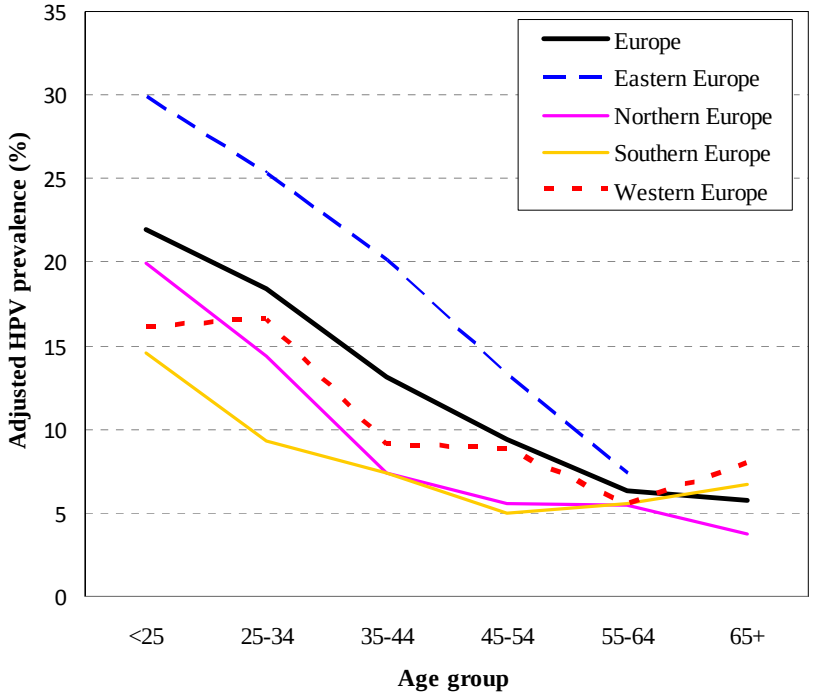
Table 13 – Odds ratio the risk of cervical cancer associated with cytological screening according to age at screening and age at diagnosis of cancer. OR is not <1 for women in age group 22-24[67]

	OR (95% CI)
Cancer diagnosed aged 25-29	
Screened age 22-24	1.11 (0.8-1.5)
Cancer diagnosed aged 35-39	
Screened age 32-34	0.55 (0.4-0.7)
Cancer diagnosed aged 45-49	
Screened age 42-44	0.37 (0.3-0.5)

3.2 Age-specific prevalence of HPV infection

In developed countries, the prevalence of HPV infections peaks shortly after onset of sexual activity and typically peaks in older teenagers and women in their early 20ies. Thereafter, the prevalence decreases progressively by age with sometimes a discrete peak around 45-55 years (Figure 17)[69-71].

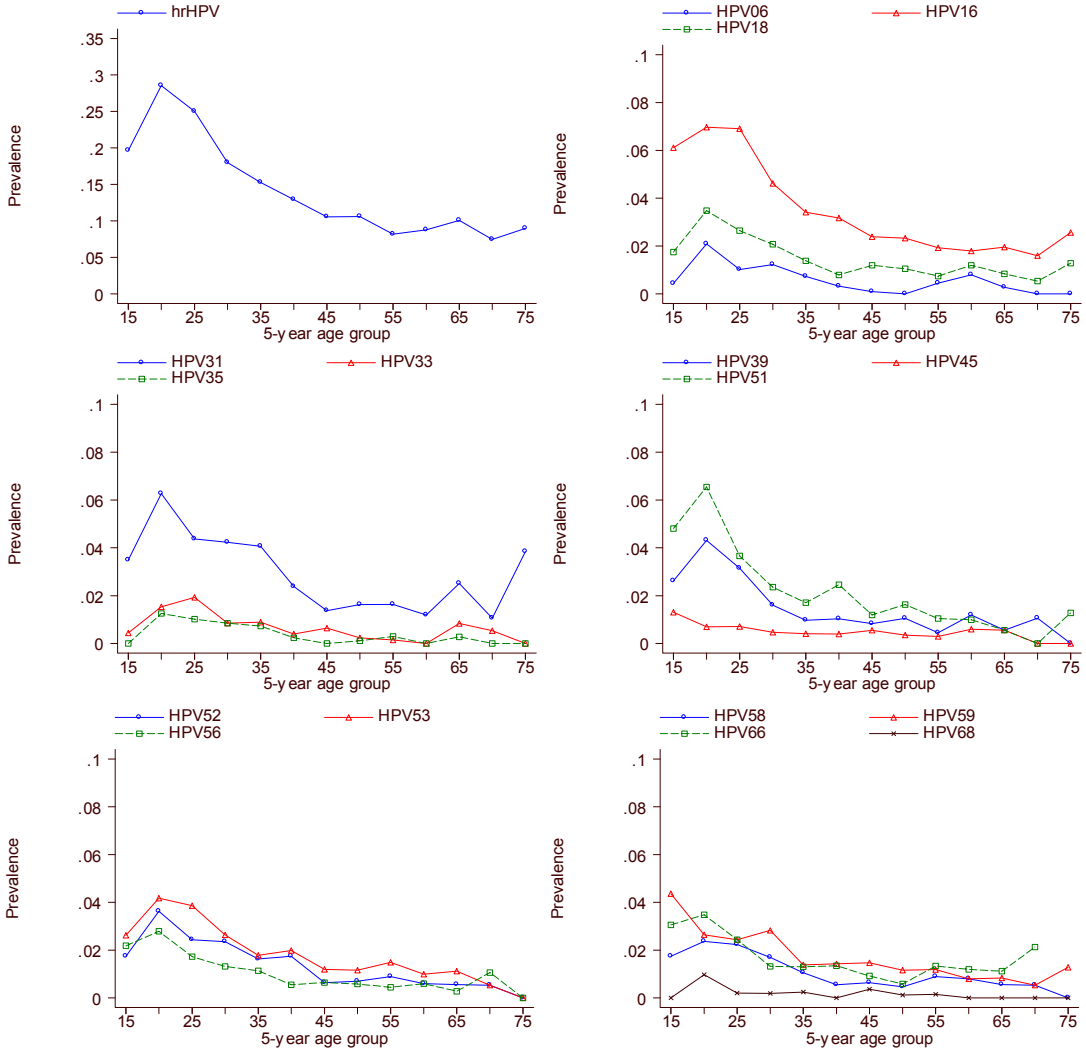
Figure 17 – Adjusted prevalence of HPV infection by age in women with normal cervical cytology, in Europe, pooled by subcontinent and for the whole of Europe



Source: Arbyn, ESGO Textbook of Gynaecological Oncology[72], adapted from Bruni, J Infect Dis 2010[69].

Figure 18 shows the age-specific prevalence of high-risk HPV and type-specific HPV infection in Belgium[73]. The shapes of the curves are as observed in most industrialized countries. The observed prevalence is rather high because the study population also included women under follow-up and because of the use of an HPV assay with high analytical sensitivity[73].

Figure 18 – Prevalence of hrHPV infection and type-specific HPV infection among women attending screening in Belgium



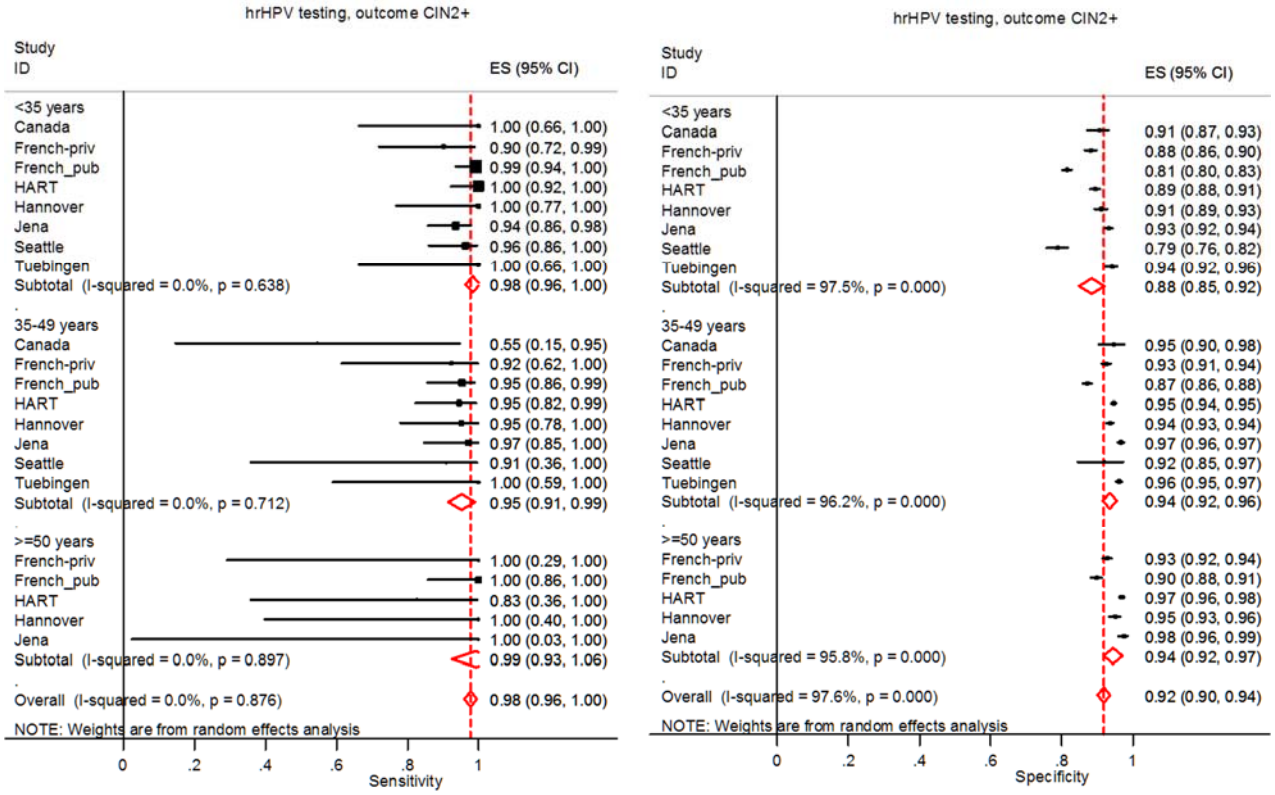
Source: Arbyn, Cancer Epidemiol Biom Prev[73].

3.3 Variation in test accuracy of cervical cytology and hrHPV DNA testing by age

Data included in a published pooled analysis of the age-specific accuracy of virological and cytological screening for cervical precancer (CIN2+ or CIN3+)[74] derived from six European[55, 57, 75-77] and two North-American studies[78, 79] were reanalyzed using a random effect model for meta-analysis. Data were aggregated in three age groups: <30 years, 30-49 year and 50 or older.

The forest plots in Figure 19 and Figure 20 show the variation of the accuracy CIN2+ of hrHPV DNA testing a cervical cytology, respectively, whereas the relative accuracy of the two tests is shown in Figure 21.

Figure 19 – Sensitivity (left) and specificity (right) of hrHPV DNA testing in cervical cancer screening, outcome CIN2+



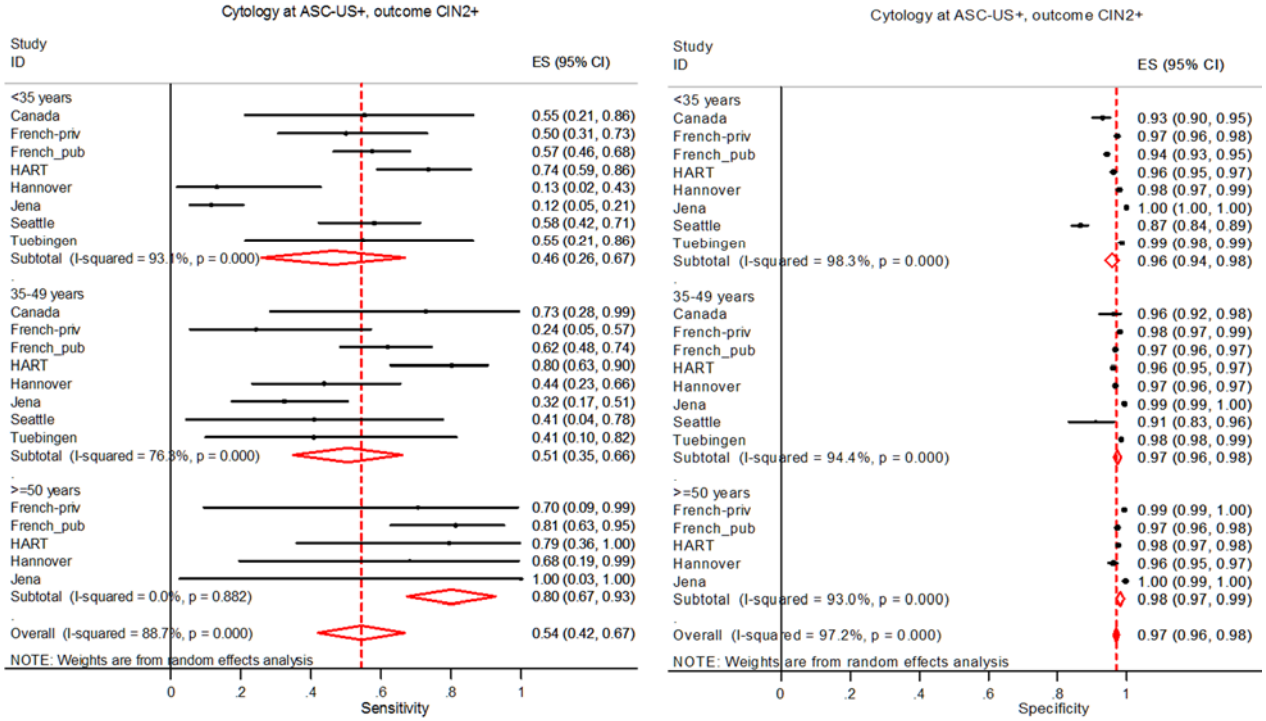
Adapted from Cuzick, IJC 2006[74].

Forest plots for the outcome CIN3+ can be requested from the Unit of Cancer Epidemiology of WIV-ISP. A summary of the pooled absolute and relative accuracy parameters for both CIN2+ and CIN3+ is presented in Table 14.

The sensitivity of hrHPV testing was homogenously high (>94%, p for heterogeneity by age group >0.10), whereas the sensitivity of cytology was low and increased significantly by age (<52% for women aged <50 years, ~80% for women of older age).

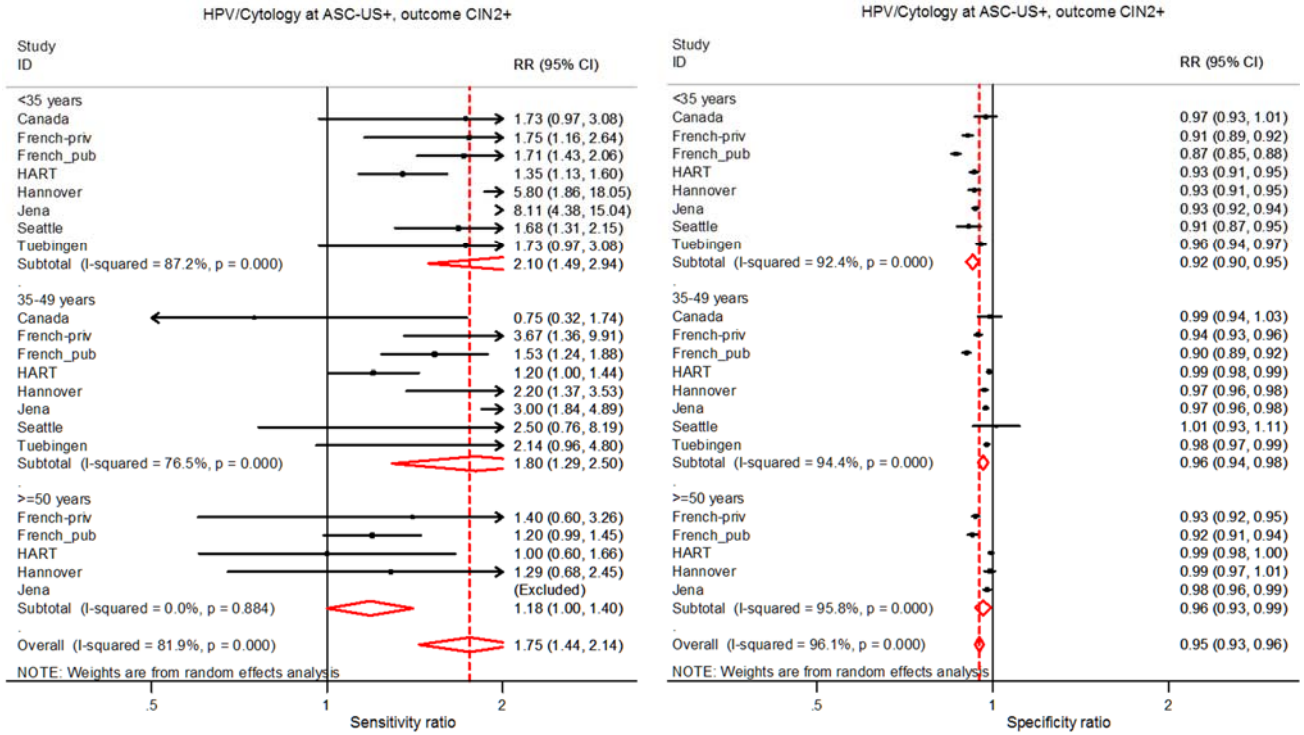
In all age-groups, the sensitivity of hrHPV DNA testing was significantly and substantially higher than that of cytology, but the contrasts decreased by age. The inter-study variability in cytology was substantially greater than that of hrHPV testing, reflecting the lower reproducibility of the former test.

Figure 20 –Sensitivity (left) and specificity (right) of cytology at cut-off ASC-US+ in cervical cancer screening, outcome CIN2+



Adapted from Cuzick, IJC 2006[74].

Figure 21 – Relative sensitivity (left) and specificity (right) of hrHPV DNA testing versus cytology at ASC-US+ to detect underlying CIN2+



Adapted from Cuzick, IJC 2006[74].

Table 14 – Sensitivity and specificity of hrHPV DNA testing and cytology (at ASC-US+) to detect CIN2+ and CIN3+ in women attending cervical cancer screening, by age group (Relative sensitivity and specificity of the two tests)

		<35 years	35-49 years	50+ years	Trend
Absolute accuracy of hrHPV DNA testing					
Sensitivity	CIN2+	98.4 (96.3-100)	95.2 (91.4-99.1)	99.3 (92.7-100.0)	0.13
	CIN3+	98.8 (96.5-100)	94.5 (89.5-99.0)	100.0 (93.2-100.0)	0.86
Specificity	CIN2+	88.4 (84.9-92.0)	93.5 (91.5-95.5)	94.4 (91.8-97.1)	<0.001
	CIN3+	86.4 (82.6-90.3)	93.1 (91.0-95.2)	94.1 (91.4-96.9)	<0.001
Absolute accuracy of cytology at ASC-US+					
Sensitivity	CIN2+	46.4 (25.9-66.8)	50.5 (34.9-66.1)	80.1 (67.5-92.7)	<0.001
	CIN3+	49.4 (29.8-69.0)	49.0 (33.3-64.6)	80.8 (67.5-94.1)	0.01
Specificity	CIN2+	95.7 (9379-97.7)	97.3 (96.2-98.4)	98.1 (96.9-99.24)	<0.001
	CIN3+	94.7 (92.2-97.1)	97.0 (95.8-98.2)	97.9 (96.6-99.2)	<0.001
Relative accuracy (hrHPV DNA vs. cytology)					
Sensitivity ratio	CIN2+	2.10 (1.49-2.94)	1.80 (1.29-2.50)	1.19 (1.00-1.40)	
	CIN3+	1.91 (1.39-2.63)	1.83 (1.29-2.59)	1.22 (1.01-1.46)	
Specificity ratio	CIN2+	0.92 (0.90-0.95)	0.96 (0.94-0.98)	0.96 (0.93-0.99)	
	CIN3+	0.91 (0.89-0.94)	0.96 (0.94-0.98)	0.96 (0.93-0.99)	

Adapted from Cuzick, IJC 2006[74].

The pooled specificity of hrHPV DNA testing and cytology increased by age: between 88% and 94%, for the former, and between 96% and 98% for the latter. The specificity of hrHPV testing always was significantly lower than that of cytology, but the contrasts decreased by age: ratio of 0.91 among women younger than 35, and 0.96 among women older than 50.

The higher relative sensitivity of hrHPV and lower specificity compared to cytology in young women may reflect the transient character of HPV infection and a certain degree of over-diagnosis[80].

Over-diagnosis was also suggested from the 2nd phase of the Italian NTCC screening trial. In this phase all women testing positive with the HC2 randomized to the experimental arm. The detection rate of CIN3+ was more than three times higher than in the cytology arm (ratio=3.1, 95%CI: 2.2-4.4) among women aged 25-34. In women aged 35-60, the relative detection rate was substantially lower (ratio= 1.68, 95% CI: 1.25-2.26)[45].

3.4 Influence of age on screening efficacy

Pooling of the individual data of four randomised clinical trials comparing HPV- with cytology-based screening, conducted in Europe, allowed addressing the effect modification by age group on screening efficacy (reduction in the incidence of invasive cervical cancer) (Table 15).

Table 15 – Relative risk or protective effect (reduction in incidence of invasive cervical cancer) in women screened with HPV testing vs cytology, according to age at enrolment

Age at enrolment (years)	RR	95% CI	I^2	p for heterogeneity (inter-study)
<30	0.98	0.19–5.20	0.00%	0.34
30-34	0.36	0.14–0.94	7.20%	0.36
35-49	0.64	0.37–1.10	0.00%	0.55
>=50	0.68	0.30–1.52	36.50%	0.21

RR= relative risk (cumulative incidence of invasive cervical cancer observed in the HPV arm compared to that observed in the cytology arm). I^2= measure of inconsistency, the percentage of total variation across studies due to inter-study heterogeneity. Source: Ronco, Lancet 2013[48].

3.5 Age-specific adverse effects related to treatment of screen-detected lesions

Data from recent meta-analyses show higher rates of adverse pregnancy outcomes in women with a prior history of excisional treatment of cervical pre-cancer than in the general population[81-83], in particular when the excision is deep or a large proportion of cervical tissue is excised[84]. Adverse pregnancy outcomes may be induced by cervical incompetence or decreased protection against ascending infections and include preterm premature rupture of the membranes, preterm delivery (<37 weeks of gestation) and low birth weight (<2500gr). Shallow excision of the transformation zone might be free of adverse obstetrical effects as suggested from recent reports where excisions probably were less aggressive[85, 86].

Age-specific birth rate and cumulative rate of excisional treatment by age are important factors allowing the estimation of the burden of adverse obstetric outcome generated by screening (see Figure 22 and Figure 23).

The increased risk of adverse obstetric outcomes should be an issue when defining start of screening, in particular when HPV-based screening is

Figure 22 – Birth rate (number of births/1000 women/year) by 5-year age group in Belgium

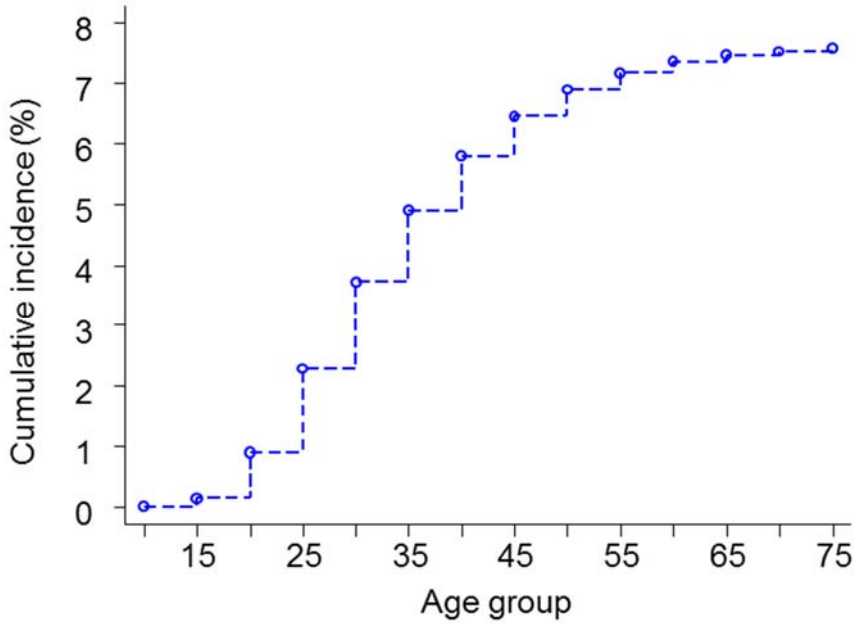
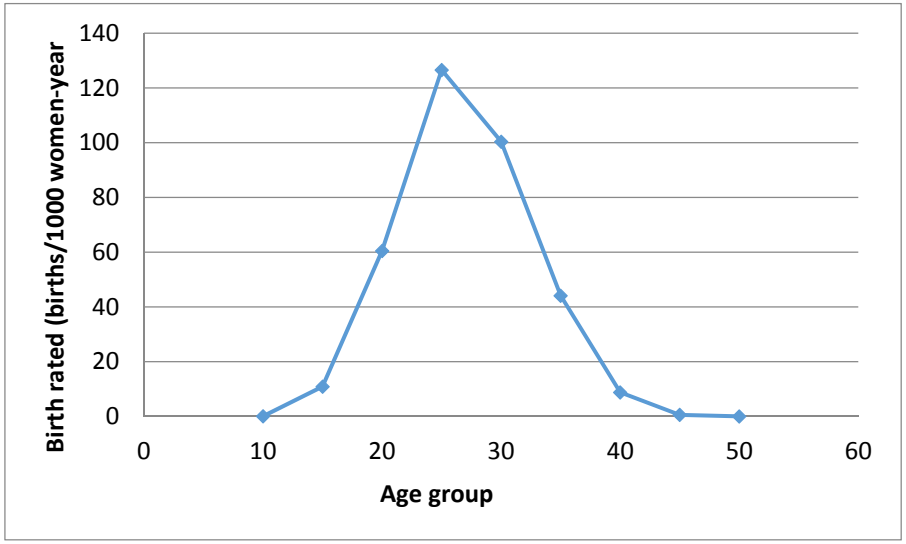


Figure 23 – Cumulative incidence of conisation up to a given age (right) in Belgium, 2002-2006



Source: Arbyn et al., IMA report[53].

3.6 Age to stop screening

There is no firm consensus on the age where cervical cancer screening can be stopped. It should be defined on the basis of the cumulative risk after one or more previous negative screening tests. One can rank the following outcomes by increasing level of evidence they provide as outlined in Table 16.

Table 16 – Low risk after previous negative screening tests, by level of importance of the outcome

1.	cumulative risk of cervical precancer or cancer (CIN2+, CIN3+ [including adenocarcinoma in situ];
2.	cumulative incidence of invasive cervical cancer;
3.	mortality from cervical cancer.

The 2008-EU guidelines recommend cytological screening up to the age of 60 with the possibility to extend beyond that age depending on available resources and the local burden of disease[32, 50, 66].

In the EU Member States, the recommended age to stop cytology-based screening varies between 59 and 69 (see Table 12). It has been proposed that regularly screened women, aged 50 or older, with successive negative cytology results have a very low risk of cervical cancer precursors later in life and could be safely discharged from further screening[87-89]. This proposition has been challenged by recent data from the Netherlands, showing that cumulative incidence of invasive cancer after 3 consecutive negative smears was similar in younger (30-44 years) and older women (45-54 years)[90]. However, unscreened or insufficiently screened older women are still at considerable risk and could benefit from screening beyond the target age range[91]. Moreover, older women treated for high-grade CIN have a higher rate of recurrence or residual disease than younger women[92]. Women with a history of CIN treatment, in general, are at risk for subsequent cervical cancer that is 2-4 times higher than in the general population and this increased risk further rises by age at diagnosis[93, 94]. A negative HPV, at the age of 50 or older, or after treatment of CIN, has been proposed as a criterion for ceasing screening or relaxing follow-up. Nevertheless, data are conflicting[95, 96]. More research is needed regarding the choice of the age limit to stop screening taking into account the screening and treatment history, the remaining healthy-life expectancy, the age-specific incidence of cervical cancer as well as age- and stage-specific survival. In organized screening, invitations cease at an upper age limit (59-65 years, in the old 15 member states of the EU). It has been proposed that regularly screened women, aged 50 or older, with successive negative cytology results have a very low risk of cervical cancer precursors later in life and could be safely discharged from further screening[87-89]. This proposition has been challenged by recent data from the Netherlands, showing that cumulative incidence of invasive cancer after 3 consecutive negative smears was similar in younger (30-44 years) and older women (45-54 years)[90]. However, unscreened or insufficiently screened older women are still at considerable risk and could benefit from screening beyond the target age range[91]. Moreover, older women treated for high-grade CIN have a higher rate of recurrence or residual disease than younger women[92]. Women with a history of CIN treatment, in general, are at risk for subsequent cervical cancer that is 2-4

times higher than in the general population and this increased risk further rises by age at diagnosis[93, 94]. A negative HPV, at the age of 50 or older, or after treatment of CIN, has been proposed as a criterion for ceasing screening or relaxing follow-up. Nevertheless, data are conflicting[95, 96]. More research is needed regarding the choice of the age limit to stop screening taking into account the screening and treatment history, the remaining healthy-life expectancy, the age-specific incidence of cervical cancer as well as age- and stage-specific survival[52].

When HPV testing is used, screening could be stopped earlier given the longer lead time compared to cytology based screening and the lower risk of acquiring new progressive infections after a negative screening test[43]. However, in the future EU guidelines, the lack of data is recognized regarding the future risk of cervical cancer after a previous negative HPV test among women older than forty. For safety reasons, no change in screening policy with respect to stopping screening can be proposed.

3.7 Conclusion

- HPV-based screening should not start before the age of 30 (lack of evidence of health benefit, high prevalence of transient infections, risk of over-diagnosis, increased risk of obstetrical adverse effects).
- HPV-based screening could allow stopping screening at earlier age than for cytology-based screening. However, by lack of data and for reasons of safety, no change in the policy regarding the upper age of the target screening population can be proposed.

4 TRIAGE OF WOMEN WITH A POSITIVE HPV TEST AT SCREENING

4.1 Introduction

Meta-analyses discussed in 1.1 have demonstrated improved sensitivity of high-risk HPV (hrHPV) DNA-based testing, compared to cytology in primary screening with respect to detection of cervical precancer which subsequently results in a lower incidence of CIN3 and cancer observed after a first screening round (reviewed in Arbyn, 2012 Vaccine[6]; and confirmed by a pooled analysis[48]). However, the higher sensitivity for CIN2+ and CIN3+, is associated with a drop in specificity, which results in a decreased cross-sectional positive predictive value (PPV) and may lead to unnecessary follow-up of screen-positive women and over-management of patients. Consequently, the triage of women with a positive hrHPV-DNA test constitutes an important clinical issue to address.

4.2 Materials and methods

4.2.1 Clinical question

In this report, diverse triage methods are evaluated that can be used to manage women with a positive hrHPV-DNA test at screening. The clinical question is: “What is the best test or combination of tests which results in the highest sensitivity for progressive cervical precancer at the lowest burden of follow-up?” The PICOS[97, 98] elements linked to this clinical question are listed in Box 2.

Box 2 – PICOS-elements

PICOS

P: women participating in virological screening for cervical cancer, having a positive hrHPV-DNA test result

I: reflex testing with biomarkers (HPV genotyping, hrHPV-mRNA testing, p16, p16/KI67, other markers) and repetition of hrHPV-DNA testing, cytology and/or or combinations thereof

C: reflex cytology triage at cut-off ASC-US

O: cross-sectional and longitudinal accuracy to detect histologically identified disease (=CIN2+,CIN3+/AIS, and cervical cancer) triage test positivity rate, referral rate for colposcopy, PPV for CIN2+ & CIN3+, risk of CIN2+, CIN3+ and cancer after negative triage testing

S: follow-up of randomised trials comparing cytology, with HPV-based screening and applying different follow-up algorithms

- complete diagnostic studies (all subjects tested with triage method and verification with the reference standard (colposcopy/biopsy))

- cohort studies applying at least two alternative triage algorithms involving verification with the reference standard if one or more positive triage test result

4.2.2 Literature Search

Studies were eligible if (1) cross-sectional and/or longitudinal triage data were available for women with a positive hrHPV screening test, and (2) verification with the golden standard (colposcopy and targeted biopsy, possibly completed with random biopsies and/or endocervical curettage) was performed on all women or women with at least one positive triage test.

Triage methods consisting of a one-step strategy or a two-step strategy were eligible. Each triage step could consist of a single test, or combined testing with two assays using an 'AND' (both tests positive) or an 'OR' (at least one test positive) approach.

4.2.3 Statistical analysis

Where possible (sufficient studies), the pooled absolute sensitivity and specificity of triage tests were estimated jointly using *metandi*, a procedure in STATA, based on the bivariate normal model for the logit transforms of sensitivity and specificity taking the intrinsic correlation between true and false-positivity rates and the variability between studies into account[99, 100].

When insufficient studies were available (<=4) absolute relative sensitivity and specificity ratios were computed independently using the STATA procedures metaprop[c] and metan[101], respectively. In this case, overall pooled measures, with 95% confidence intervals were calculated using random effects models[102]. The statistical heterogeneity was assessed by the p-value for heterogeneity (following a chi2 distribution) as well as by the I^2 statistic, which measures the variation across studies that is due to inter-study heterogeneity.

Anticipating on scarcity of data (triage scenarios only assessed in one study), we also considered estimating the absolute accuracy of a given triage strategy by using the absolute sensitivity and specificity of the reference triage strategy (reflex cytology at cut-off ASC-US+) multiplied by the relative sensitivity and specificity of a given strategy, as assessed from

[c] Metaprop is a statistical procedure in STATA developed at the Unit of Cancer Epidemiology (IPH Brussels) to pool proportions based on binomial distributions.

a bivariate normal model with triage strategy as a covariate, using the SAS macro metadas[103].

- $Sensitivity_{strategy\ X}$ = pooled $Sensitivity_{ref}$ * modeled Relative $Sensitivity_{x\ versus\ ref}$
- $Specificity_{strategy\ X}$ = pooled $Specificity_{ref}$ * modeled Relative $Specificity_{x\ versus\ ref}$.

This method is built on the general finding that ranges of variability on relative accuracy are smaller than on absolute accuracy.

4.3 Results

4.3.1 Literature retrieval

For the analysis presented here, we included data from controlled trials conducted in population-based, organized screening programs. Based on this criterion, seven large trials were identified, which incorporated virological testing in primary screening. These seven trials comprised six European (NTCC[26, 104-106], ARTISTIC[25], SWEDESCREEN[34], VUSA[36], POBASCAM[107], and PUBLIC HEALTH TRIAL FINLAND[108]) and one American trial (ATHENA[38]). Since the data for the Italian NTCC trial, were separated in four reports[26, 104-106], a total of ten reports were found eligible, containing accuracy data for diverse triage strategies in the management of women with a positive primary screening hrHPV-DNA test.

The study characteristics of the included reports are listed in Table 17. Cross-sectional triage data were extracted for NTCC, SWEDESCREEN, ATHENA, and PUBLIC HEALTH TRIAL FINLAND. Longitudinal data were extracted for NTCC, ARTISTIC, VUSA and POBASCAM, comprising three, three, two and four years of follow-up, respectively. Five studies[26, 38, 104-106] had a complete design, referring all hrHPV-positive women to verification with the golden standard, while in the other five studies an incomplete design was applied, which means that only triage positive women were submitted to the golden standard.

Table 17 – Study characteristics of the included studies

Trial name	Study	Country	Population	Follow-up	Gold standard	Triage tests
ARTISTIC (round 1)	Kitchener 2009[25]	UK	Screening population. 20-64y	36m	Colposcopy + targeted biopsies. - If LSIL+, immediate verification. If ASC-US or LSIL, repeat cytology (6m, 12m) and verification if LSIL+. If <ASC-US, repeat HPV testing (12m, 24m) and verification if positive.	LBC (ThP) HC2
Athena	Castle 2011[38]	USA	Screening population. ≥25y	4m	Colposcopy + targeted biopsies or ECC. - All participants.	LBC (ThP) Linear Array Cobas(HPV1618)
NTCC	Ronco 2006[26, 104]	Italy	Screening population. 25-34y[104] 35-60y[26]	6m	Colposcopy + targeted biopsies. If ≥ 35 y: all participants. <35y: colposcopy referral if ASCUS+; repeat testing if cyto-/HPV+ & referral if 2nd testing (cyto/HPV) showed a + result.	LBC (ThP)
NTCC-2	Carozzi 2008[105]	Italy	Screening population. 25-60y	6m	Colposcopy + targeted biopsy. - All participants.	p16
NTCC-2	Carozzi 2013[106]	Italy	Screening population. 25-60y	36m	Colposcopy + targeted biopsy. - All participants.	p16
Pobascam	Dijkstra 2013[107]	The Netherlands	Screening population. 29-61y	48m	Colposcopy + targeted biopsies. - If HSIL+, immediate verification. If <HSIL, repeat HPV and cytology (6m, 18m) and verification if ASC-US+ at 6m, or ASC-US+ and/or hrHPV+ at 18m. If <ASC-US,	CP PCR (GP5+/6+) and RLB
Public Health Trial Finland	Leinonen 2013[108]	Finland	Screening population. 25-65y	12m	Colposcopy + targeted biopsies. - If LSIL+, immediate verification. If <LSIL, repeat (12, 24m).	CP PCR Luminex
SWEDESCREEN	Naucler 2009[34]	Sweden	Screening population. 32-38y	20m	Colposcopy + targeted biopsies or 2 random biopsies. - If ASC-US+, immediate verification or repeat cytology (depending on local practices. If <ASC-US, repeat HPV (12m) and verification if type-specific persistence.	CP PCR (GP5+/6+)
Vusa	Rijkaart 2012[36]	The Netherlands	Screening population. 30-60y	24m	Colposcopy + targeted biopsies. - If ASC-US+, immediate verification. If <ASC-US, repeat HPV and cytology (12m, 24m) and verification if ASC-US+ at 12m, or ASC-US+ and/or HPV+ at 24m.	CP PCR (GP5+/6+) and RLB

Abbreviations: ASC-US+, atypical squamous cells of undetermined significance; CP, conventional Pap smear; ECC, endocervical curettage; HSIL, high-grade squamous intraepithelial lesions or worse; HC2, Hybrid Capture 2 assay; LBC, liquid based cytology; LSIL+, low-grade squamous intraepithelial lesions or worse; PCR, polymerase chain reaction; RLB, reverse line blotting; ThP, ThinPrep.

4.3.2 Absolute accuracy of cytology and/or hrHPV-DNA based triage algorithms

Diverse triage algorithms were available in the included studies, ranging from one-step to two-step triage strategies with diverse methods such as cytology, repeat hrHPV testing, HPV genotyping, and/or p16 cytoimmunochemistry. In most studies, the available data was detailed enough enabling extraction of absolute and uncorrected values for true-positives (TP) and –negatives (TN) , and false-positives (FP) and –negatives (FN) for all or a subset of triage algorithms. Some studies only allowed extraction of a corrected accuracy measures (e.g. sensitivity, specificity, PPV, NPV, etc.) which were adjusted for non-compliance to the study protocol. Meta-analytic pooling was performed using the available values for TP, FN, FP, and TN.

4.3.2.1 Triage with reflex cytology (cut-off ASC-US+)

Eight studies contained uncorrected absolute numbers of true- and false-positive and negative results for one-step triage with reflex cytology at cut-off ASC-US+[25, 26, 34, 36, 38, 104, 107, 108]. Two reports by Ronco et al. (NTCC-1)[26, 104] were combined for women between 35-60y and women below 35y, respectively. The pooled sensitivity and specificity for reflex cytology at cut-off ASC-US+ to detect CIN2+ was 79.5% (95% CI: 65.2-90.8%) and 79.1% (95% CI: 73.0-84.6%), respectively (Figure 25 and Figure 26). To detect CIN3+, the pooled sensitivity and specificity of reflex cytology at cut-off ASC-US+ was 82.0% (95% CI: 66.9-93.4%) and 72.3% (95% CI: 67.0-77.3%), respectively (Figure 24).

In Table 18, the absolute accuracy measures for the different triage algorithms are listed.

Accuracy data for the addition of a second triage step after six months to manage women who had a negative cytology triage test at baseline, were available only for the POBASCAM trial[107]. In POBASCAM, the sensitivity of cytological triage at ASC-US+ for CIN3+ at baseline was 82% and by adding a second triage, sensitivity increased to 96%, 100% and 100% for, with the 2nd triage test being ASC-US+ cytology, hrHPV testing, or ASC-US+ cytology with hrHPV DNA testing. At the same time, the specificity decreased from 72% to 57%, 30%, or 28%. The PPV decreased from 35% to 23%, the NPV increased 97.5% to 100% and the referral rate increased from 31% to 75% (see Table 18). Considering the outcome CIN2+, the sensitivity increased from 75% (baseline ASC-US+ triage) to 93%, 99.5% or 99.7%, whereas the specificity decreased from 88% to 80%, 44% or 41%, by adding the one of the considered 2nd triage tests (see Table 18).

Figure 24 – sROC plots of the sensitvity as a function of the specificity of reflex cytology at cut-off ASC-US to detect CIN2+ (left) and CIN3+ (right) in the triage of women with a positive hrHPV-DNA screening test

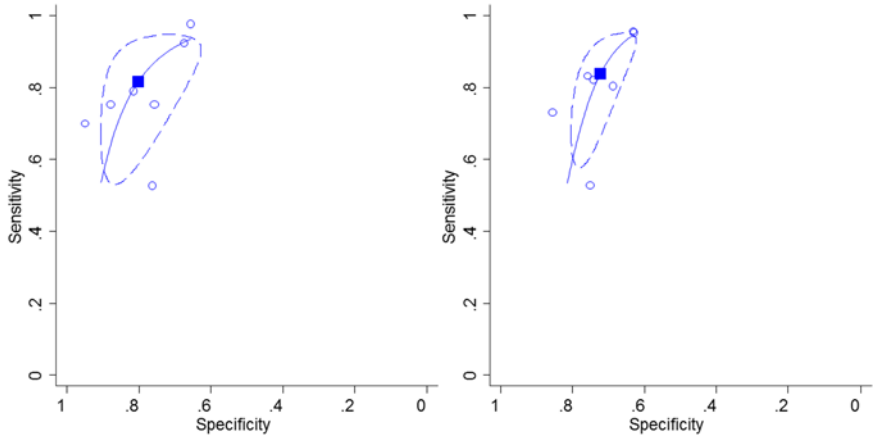
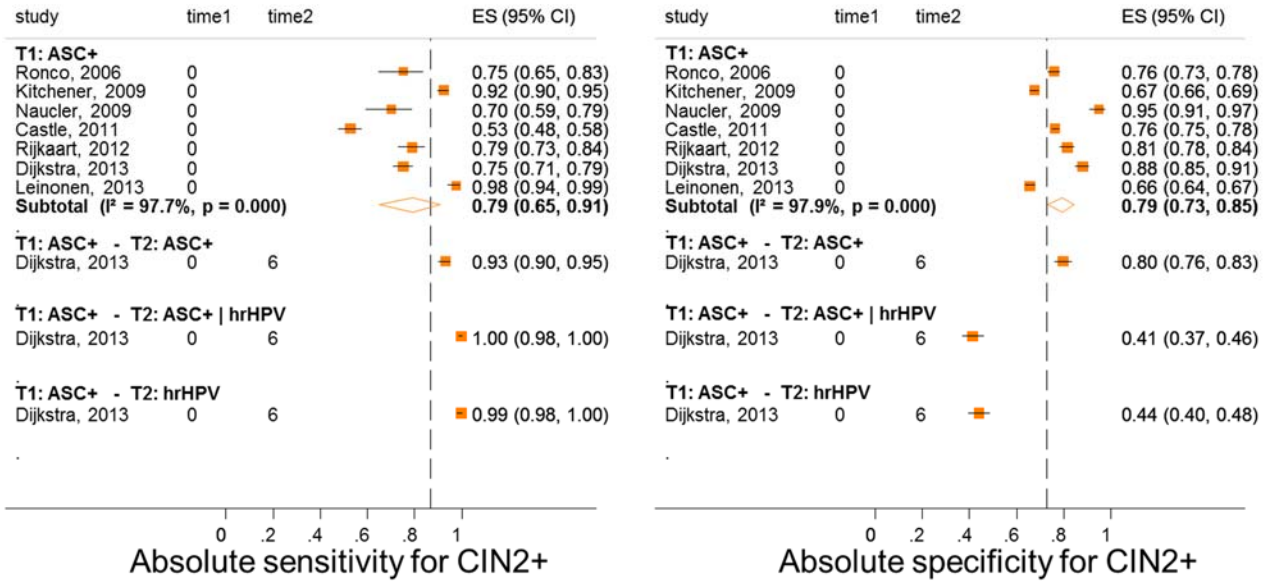
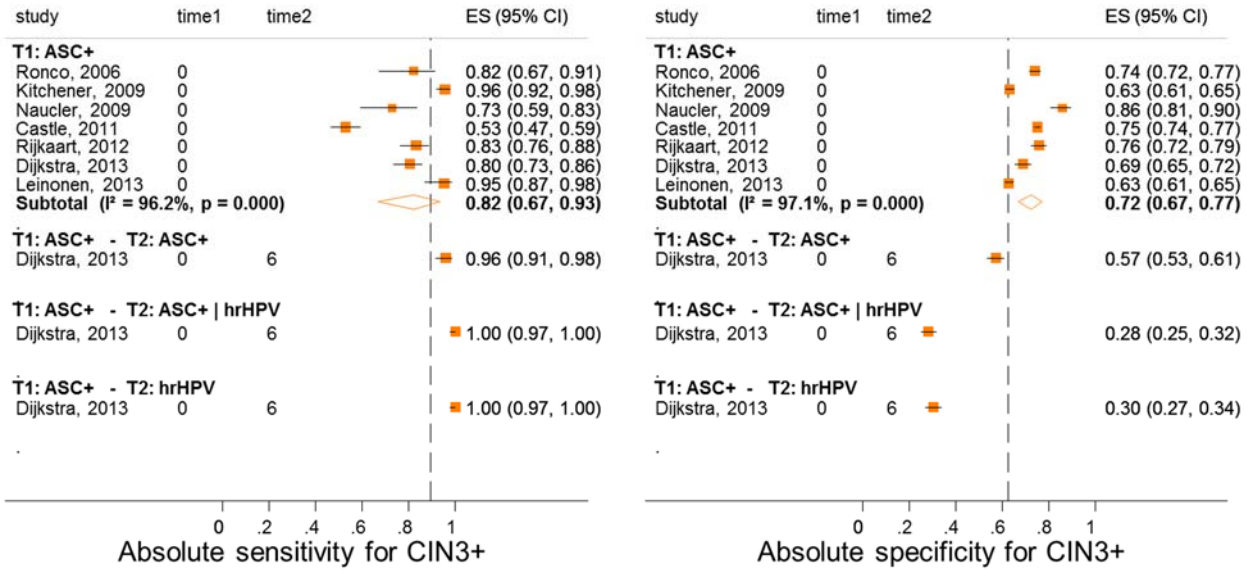


Figure 25 – Meta-analysis of the absolute sensitivity and specificity to detect CIN2+ of four triage algorithms with reflex cytology (cut-off: ASC-US) as first triage, time1 and time2 correspond to the timing of the triage step (in months)



Abbreviations: |, 'OR'; ASC+, atypical squamous cells or worse; CI, confidence interval; I², percentage of total variation across studies due to heterogeneity; hrHPV, high-risk human papillomavirus; p, test for inter-study heterogeneity.

Figure 26 – Meta-analysis of the absolute sensitivity and specificity to detect CIN3+ of four triage algorithms with reflex cytology (cut-off: ASC-US) as first triage, time1 and time2 correspond to the timing of the triage step (in months)



Abbreviations: |, 'OR'; ASC+, atypical squamous cells or worse; CI, confidence interval; I², percentage of total variation across studies due to heterogeneity; hrHPV, high-risk human papillomavirus; p, test for inter-study heterogeneity.

Table 18 – Absolute sensitivity, specificity, positive and negative predictive values, and referral rate for triage with reflex cytology at cutoff ASC-US+ combined or not with second triage step among women with a positive hrHPV test

Triage1	Triage2	Number of studies	Outcome	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	Referral rate% (95% CI)
ASC-US+		7*	CIN3+	82.0 (66.9-93.4)	72.3 (67.0-77.3)	22.9 (13.7-33.6)	97.5 (95.0-99.1)	32.0 (27.0-37.3)
ASC-US+	ASC-US+	1	CIN3+	95.9 (91.4-98.1)	57.2 (53.5-60.8)	32.2 (28.0-36.7)	98.5 (96.8-99.3)	52.1 (48.8-55.5)
ASC-US+	hrHPV	1	CIN3+	100 (97.5-100)	30.2 (26.9-33.7)	23.3 (20.2-26.8)	100 (98.2-100)	75.1 (72.0-77.9)
ASC-US+	ASC-US+ | hrHPV	1	CIN3+	100 (97.5-100)	28.2 (25.0-31.7)	22.8 (19.7-26.2)	100 (98.1-100)	76.7 (73.7-79.4)
ASC-US+		7	CIN2+	79.5 (65.2-90.8)	79.1 (73.0-84.6)	44.8 (27.2-63.1)	94.3 (89.4-97.8)	32.0 (27.0-37.3)
ASC-US+	ASC-US+	1	CIN2+	93.0 (89.9-95.2)	79.8 (75.9-83.2)	78.2 (74.1-81.8)	93.6 (90.8-95.6)	52.1 (48.8-55.5)
ASC-US+	hrHPV	1	CIN2+	99.5 (98.1-99.9)	44.0 (39.6-48.5)	58.1 (54.2-61.9)	99.1 (96.6-99.7)	75.1 (72.0-77.9)
ASC-US+	ASC-US+ | hrHPV	1	CIN2+	99.7 (98.5- 100)	41.3 (36.9-45.7)	57.0 (53.2-60.8)	99.5 (97.2-99.9)	76.7 (73.7-79.4)

** For comparison in Dijkstra et al 2013: the accuracy measure of triage with ASC-US+ cytology for CIN3+ SE=80%, SP=69%, PPV=35%, NPV=94%, referral rate=31%; and for CIN2+ SE=75%, SP=88%, PPV=83%, NPV=82%.*

4.3.3 Triage with a combination of reflex cytology (cut-off ASC-US+) and HPV16 or HPV1618 genotyping

From the POBASCAM and ATHENA trials, data could be extracted on reflex triage with a combination of cytology (cut-off ASC-US+) and HPV16 or HPV1618 genotyping, either using an 'OR' approach (one or both tests positive)[38, 107] or an 'AND' approach (both tests positive)[38]. In Table 19, the absolute accuracy measures for the different triage algorithms are listed.

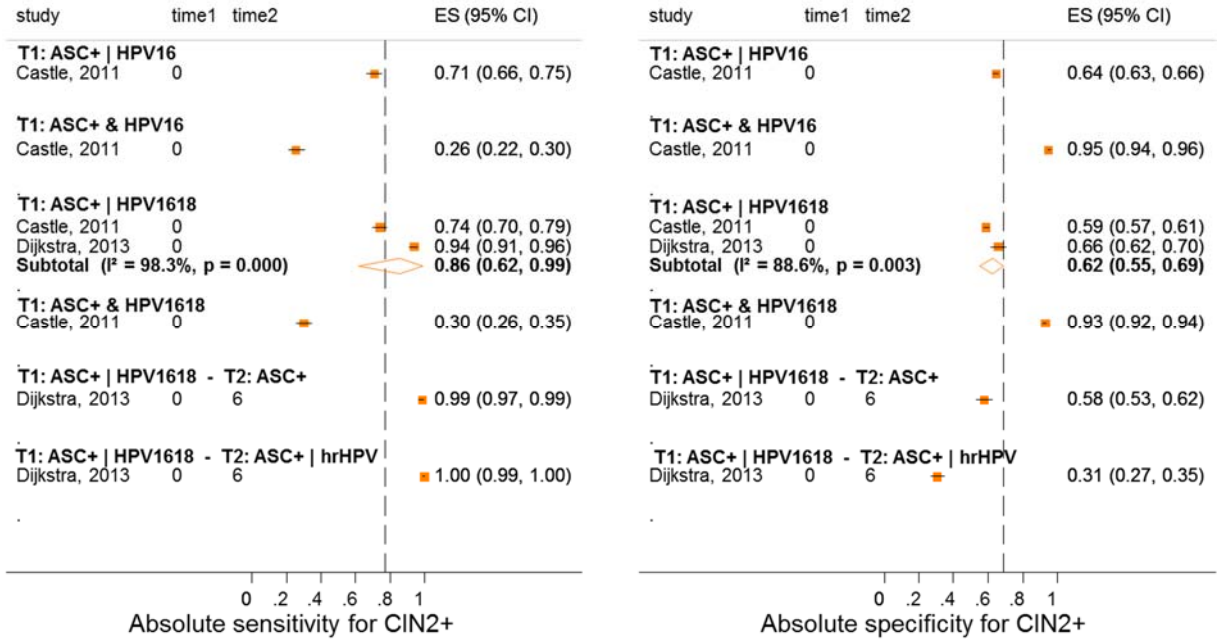
Based on these two studies, the pooled sensitivity and specificity of reflex triage with cytology (ASC-US+) or HPV1618 genotyping to detect CIN2+ was 85.7% (95% CI: 61.9-98.9%) and 62.1 (95% CI: 55.1-68.9%), respectively (Figure 27). To detect CIN3+, the pooled sensitivity and specificity were 89.6% (95% CI: 64.5-100.0%) and 52.8% (95% CI: 42.6-62.8%), respectively (Figure 28). Adding a second triage step using cytology (ASC-US+) or a combination of cytology and hrHPV-DNA testing resulted in a 13-14% gain in sensitivity for CIN2+ (98.7% [95%CI: 96.9-99.4%] and 100% [95% CI: 99.0-100%, respectively], and a ~2% gain in NPV (98.2% [95% CI: 95.9-99.2%] and 100% [95% CI: 97.4-100%], respectively). Referral rate increased up to 67.0% (95% CI: 63.8-70.1%) and 82.9% (95% CI: 80.2-85.3%) when the second triage step was cytology or combined cytology-hrHPV respectively. Given the large contrast between ATHENA and POBASCAM, an intra-study (POBASCAM) comparison is appropriate. In POBASCAM, reflex triage with ASC-US+ cytology and HPV1618 genotyping reached a sensitivity for CIN2+ of 94.1% (95% CI: 91.2-96.1%). Adding a second triage step using cytology (ASC-US+) or a combination of cytology and hrHPV-DNA testing resulted in a 5-6% gain in sensitivity for CIN2+ (reaching 99% and 100%, respectively), and a 5-6% gain in NPV (98% and 100%, respectively). Referral rate increased up to 67% and 83% when the second triage step was cytology or combined cytology-hrHPV respectively. The accuracy of reflex ASC-US+ combined with HPV1618

genotyping reached a high sensitivity for CIN3+ (97%), adding a 2nd triage step resulted in a sensitivity of 99-100% but this resulted in a specificity loss of 18-37%.

In a triage algorithm where both cytology (ASC-US+) and the HPV1618 genotyping test had to be positive, the sensitivity dropped considerably (30.0% [95% CI: 25.6-34.8%] for CIN2+, and 34.1%[95% CI: 28.6-40.2%] for CIN3+), while the specificity increased (92.9% [95% CI: 91.9-93.7%] for CIN2+, and 92.3% [95% CI: 91.3-93.1%] for CIN3+).

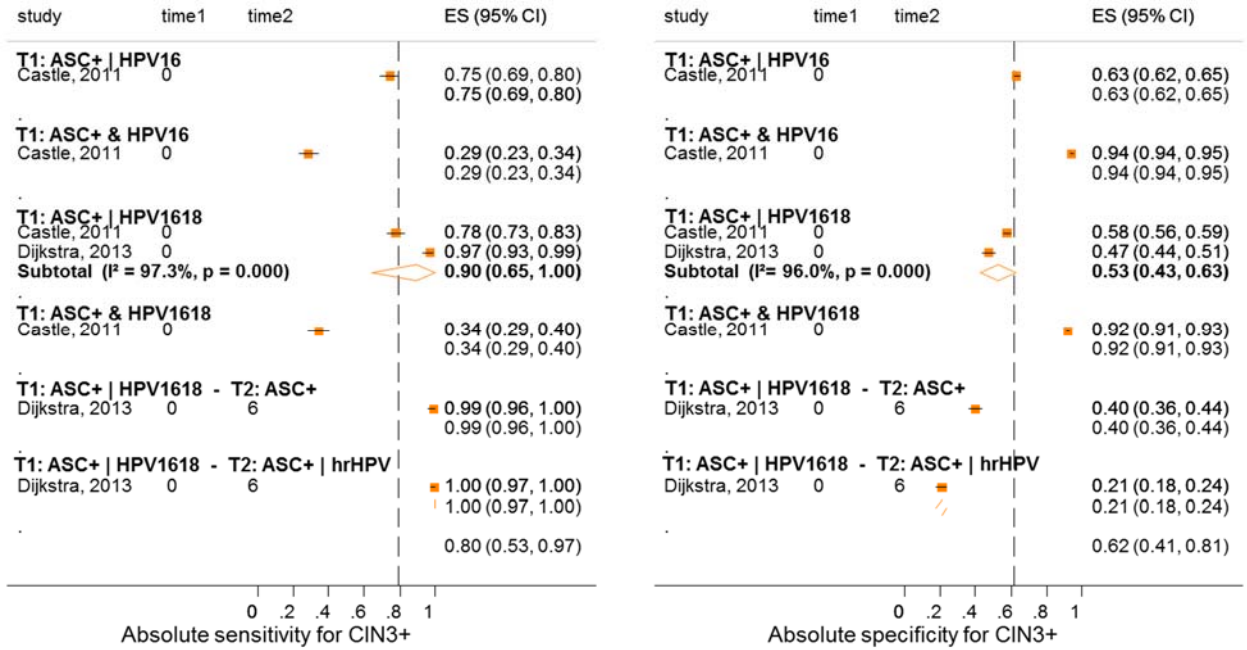
The ATHENA trial contained data on accuracy of triage with a combination of cytology (ASC-US+) and HPV16 genotyping[38]. Compared to related triage algorithms that use HPV1618 genotyping, sensitivity was 3% lower using the 'OR' approach, and 4-5% lower using the 'AND' approach.

Figure 27 – Meta-analysis of the absolute sensitivity and specificity to detect CIN2+ of six triage algorithms with a combination of reflex cytology (cut-off: ASC-US+) and HPV16 or HPV1618 genotyping as first triage, time1 and time2 correspond to the timing of the triage steps (in months)



Abbreviations: |, 'OR'; &, 'AND', ASC+, atypical squamous cells or worse; CI, confidence interval; I², percentage of total variation across studies due to heterogeneity; hrHPV, high-risk human papillomavirus; p, test for inter-study heterogeneity.

Figure 28 – Meta-analysis of the absolute sensitivity and specificity to detect CIN3+ of six triage algorithms with a combination of reflex cytology (cut-off: ASC+) and HPV16 or HPV1618 genotyping as first triage, time1 and time2 correspond to the timing of the triage step (in months)



Abbreviations: |, 'OR'; &, 'AND', ASC+, atypical squamous cells or worse; CI, confidence interval; I², percentage of total variation across studies due to heterogeneity; hrHPV, high-risk human papillomavirus; p, test for inter-study heterogeneity.

Table 19 – Absolute sensitivity, specificity, positive and negative predictive values, and referral rate of reflex cytology (ASC-US+) combined with HPV16 or HPV1618 genotyping to triage women with a positive hrHPV test

Triage1	Triage2	Number of studies	Outcome	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	Referral rate% (95% CI)
ASC-US+|HPV1618		2*	CIN3+	89.6 (64.5-100)	52.8 (42.6-62.8)	19.7 (6.9-37.0)	97.9 (96.1-99.2)	52.6 (37.3-67.5)
ASC-US+&HPV1618		1	CIN3+	34.1 (28.6-40.2)	92.3 (91.3-93.1)	25.5 (21.2-30.4)	94.8 (93.9-95.5)	9.6 (8.7-10.6)
ASC-US+|HPV1618	ASC-US+	1	CIN3+	99.3 (96.3-99.9)	39.8 (36.3-43.5)	25.9 (22.5-29.7)	99.6 (98.0-99.9)	67.0 (63.8-70.1)
ASC-US+|HPV1618	ASC-US+|hrHPV	1	CIN3+	100 (97.5-100)	20.8 (17.9-23.9)	21.1 (18.3-24.3)	100 (97.4-100)	82.9 (80.2-85.3)
ASC-US+|HPV16		1	CIN3+	74.6 (68.9-79.6)	63.3 (61.7-65.0)	13.6 (11.9-15.5)	97.0 (96.2-97.6)	39.4 (37.8-41.0)
ASC-US+&HPV16		1	CIN3+	28.6 (23.3-34.4)	94.4 (93.6-95.2)	28.5 (23.3-34.3)	94.5 (93.6-95.2)	7.2 (6.4-8.1)
ASC-US+|HPV1618		2*	CIN2+	85.7 (61.9-98.9)	62.1 (55.1-68.9)	42.0 (3.2-88.8)	94.6 (93.2-95.9)	52.6 (37.3-67.5)
ASC-US+&HPV1618		1	CIN2+	30.0 (25.6-34.8)	92.9 (91.9-93.7)	33.8 (29.0-39.0)	91.6 (90.6-92.5)	9.6 (8.7-10.6)
ASC-US+|HPV1618	ASC-US+	1	CIN2+	98.7 (96.9-99.4)	57.7 (53.2-62.0)	64.6 (60.5-68.4)	98.2 (95.9-99.2)	67.0 (63.8-70.1)
ASC-US+|HPV1618	ASC-US+|hrHPV	1	CIN2+	100 (99.0-100)	30.5 (26.6-34.8)	52.9 (49.2-56.6)	100 (97.4-100)	82.9 (80.2-85.3)
ASC-US+|HPV16		1	CIN2+	71.1 (66.3-75.4)	64.4 (62.7-66.1)	19.6 (17.6-21.7)	94.8 (93.8-95.7)	39.4 (37.8-41.0)
ASC-US+&HPV16		1	CIN2+	25.8 (21.6-30.4)	95.0 (94.2-95.7)	38.7 (32.9-44.9)	91.3 (90.3-92.2)	7.2 (6.4-8.1)

** In Dijkstra 2013, the performance parameters of triage with reflex testing with ASC-US+ cytology and HPV1618 testing for CIN2+ were: SE=94.1%, SP=65.9%, PPV=68.3%, NPV=93.4% and referral rate=60.4%; and for CIN3+: SE=97.3%, SP=47.4%, PPV=28.2%, NPV=98.8%.*

4.3.4 *Triage with reflex cytology (cut-off LSIL+) and combinations with HPV16 or HPV1618 genotyping*

Four studies were identified which provided accuracy estimates for reflex triage with LSIL+ cytology, whereas for reflex LSIL+ triage combined with genotyping for HPV16 or HPV1618 only the ATHENA trial provided accuracy data.

The pooled sensitivity and specificity to detect CIN2+ was 68.4% (95% CI: 41.5-90.0%) and 86.8% (95% CI: 83.4-89.8%), respectively (Figure 29). The pooled sensitivity and specificity to detect CIN3+ was 70.4% (95% CI: 42.9-91.7%) and 84.3% (95% CI: 80.1-88.1%), respectively (Figure 30).

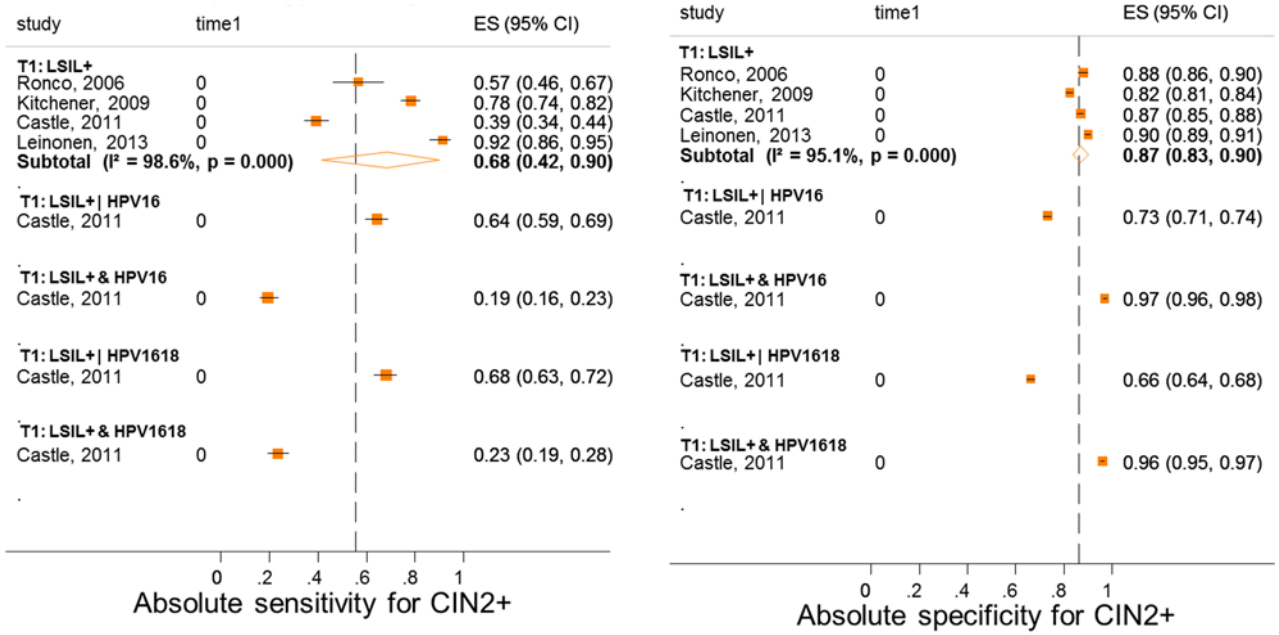
In Table 20, the absolute accuracy measures for the different triage algorithms are listed.

Comparing the pooled accuracy estimates for LSIL+ triage with those for LSIL+ combined with HPV1618 genotyping resulted in only a small gain in sensitivity for CIN3+ (from 70% to 72%)) but resulted in a drop in specificity (from 84% to 65%) and a doubled referral rate (from 18% to 38% (Table 20). In contrast, if both tests had to be positive, the referral rate dropped considerably (6.2% [95% CI: 5.4-7.0%] for CIN3+), but a significant lower sensitivity (27.4% [95% CI: 22.2-33.2%] for CIN3+) combined with a lower NPV (94.4% [95% CI: 93.6-95.2%] for CIN3+) was observed.

Given the high variability among the four studies that contributed data for LSIL+ triage, an intra-study (ATHENA) comparison might be more appropriate to appreciate the change in accuracy for adding HPV1618 genotyping to reflex LSIL+ cytology. This intra-study comparison shows a substantial gain in sensitivity (29% for CIN2+, 32% for CIN3+) and drop in specificity (21% for CIN2+ and CIN3+).

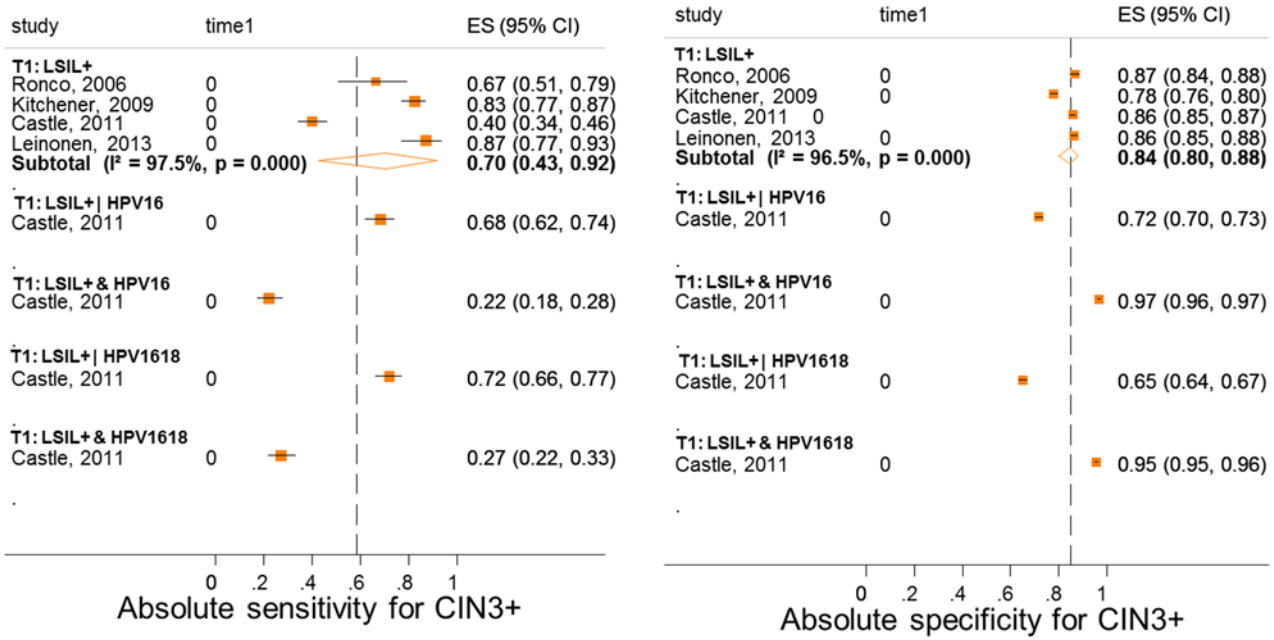
When comparing triage algorithms that use HPV16 genotyping versus related triage algorithms that use HPV1618 genotyping, the former results in approximately 5% sensitivity loss, but a 7% gain in specificity.

Figure 29 – Meta-analysis of the absolute sensitivity and specificity to detect CIN2+ of five triage algorithms with reflex cytology (cut-off: LSIL+) and HPV16 or HPV1618 genotyping, time1 corresponds to the timing of the triage step (in months)



Abbreviations: |, 'OR'; CI, confidence interval; I², percentage of total variation across studies due to heterogeneity; hrHPV, high-risk human papillomavirus; LSIL+, low-grade squamous intraepithelial lesions; p, test for inter-study heterogeneity.

Figure 30 – Meta-analysis of the absolute sensitivity and specificity to detect CIN3+ of five triage algorithms with reflex cytology (cut-off: LSIL+) and HPV16 or HPV1618 genotyping, time1 corresponds to the timing of the triage step (in months)



Abbreviations: |, 'OR'; CI, confidence interval; I², percentage of total variation across studies due to heterogeneity; hrHPV, high-risk human papillomavirus; LSIL+, low-grade squamous intraepithelial lesions; p, test for inter-study heterogeneity.

Table 20 – Absolute sensitivity, specificity, positive and negative predictive values, and referral rate of reflex cytology (LSIL+) and combinations with HPV16 or HPV1618 genotyping to triage women with a positive hrHPV test

Triage1	Number of studies	Outcome	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	Referral rate% (95% CI)
LSIL+	**4***	**CIN3+**	**70.4 (42.9-91.7)**	**84.3 (80.1-88.1)**	**17.7 (12.9-23.1)**	**98.2 (95.5-99.7)**	**18.2 (13.1-23.9)**
LSIL+ | HPV1618	1	CIN3+	72.2 (66.4-77.4)	65.2 (63.5-66.8)	13.9 (12.1-15.8)	96.8 (96.0-97.5)	37.5 (35.9-39.1)
LSIL+ & HPV1618	1	CIN3+	27.4 (22.2-33.2)	95.5 (94.7-96.1)	31.9 (26.1-38.4)	94.4 (93.6-95.2)	6.2 (5.4-7.0)
LSIL+ | HPV16	1	CIN3+	68.3 (62.3-73.7)	71.8 (70.2-73.3)	15.8 (13.7-18.1)	96.7 (95.9-97.3)	31.1 (29.6-32.6)
LSIL+ & HPV16	1	CIN3+	22.2 (17.5-27.8)	96.6 (95.9-97.1)	33.3 (26.6-40.8)	94.1 (93.3-94.9)	4.8 (4.1-5.6)
LSIL+	**4***	**CIN2+**	**68.4 (41.5-90.0)**	**86.8 (83.4-89.8)**	**33.4 (24.6-42.8)**	**96.4 (92.2-99.0)**	**18.2 (13.1-23.9)**
LSIL+ | HPV1618	1	CIN2+	67.9 (63.0-72.4)	66.2 (64.5-67.8)	19.6 (17.6-21.9)	94.4 (93.4-95.3)	37.5 (35.9-39.1)
LSIL+ & HPV1618	1	CIN2+	23.2 (19.2-27.7)	95.9 (95.1-96.5)	40.7 (34.4-47.4)	91.1 (90.1-92.0)	6.2 (5.4-7.0)
LSIL+ | HPV16	1	CIN2+	64.2 (59.3-68.9)	72.9 (71.3-74.5)	22.4 (20.0-25.0)	94.4 (93.4-95.2)	31.1 (29.6-32.6)
LSIL+ & HPV16	1	CIN2+	19.2 (15.6-23.5)	97.0 (96.3-97.5)	43.5 (36.2-51.0)	90.8 (89.8-91.7)	4.8 (4.1-5.6)

** In Castle 2011, the performance parameters of triage with reflex testing with LSIL+ cytology for CIN2+ were: SE=39.2%, SP=86.7%, PPV=26.4%, NPV=92.1% and referral rate=16.1%; and for CIN3+: SE=40.1%, SP=85.8%, PPV=17.9%, NPV=94.9%.*

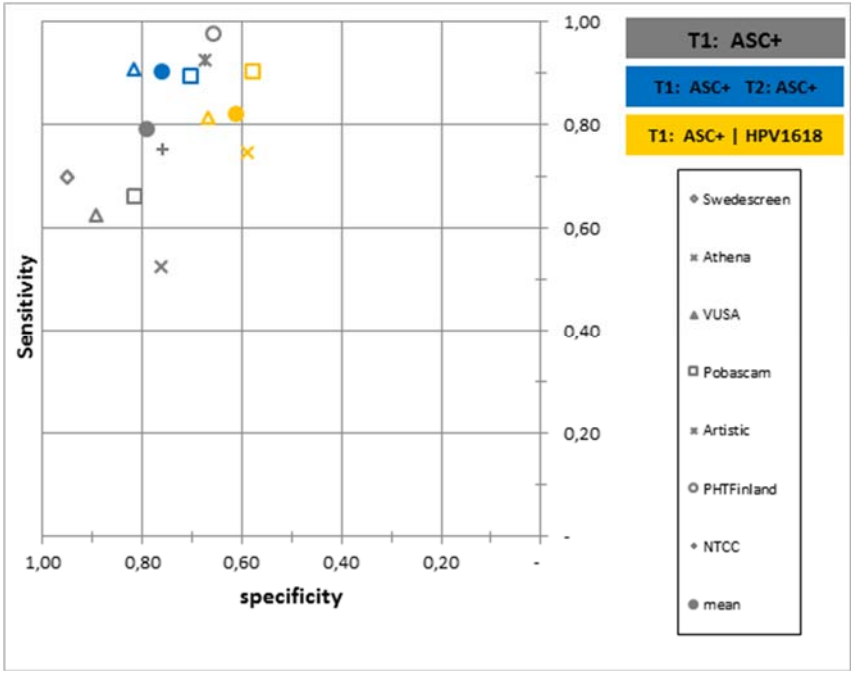
4.3.5 *Joint variation of sensitivity and specificity of 3 triage strategies*

In Figure 31, the variation of the sensitivity and specificity of three sensitive triage strategies are displayed in ROC space: 1) reflex cytology (ASCUS+) triage (green); 2) reflex cytology (ASCUS+) triage (green) completed with 2nd cytology (ASCUS+) triage if reflex triage was negative (blue); 3) reflex triage with cytology and HPV1618 genotyping (yellow). The accuracy measures are based on estimates adjusted for non-compliance derived from the published papers, and therefore do not always correspond to values that were calculated based on the number of absolute true- and false-positives and –negatives, unadjusted for follow-up compliance. By lack of absolute values of the adjusted accuracy parameters, no statistical inference can be made. For each displayed triage scenario, the simple average sensitivity and specificity was computed allowing a rough estimation of the pooled accuracy measures. Within the framework of the COHEAHR project, funded by the 7th Framework Programme of DG Research of the EU, authors are being contacted to obtain non-available absolute numbers which subsequently will be used for a formal meta-analysis of the accuracy to predict the outcomes of alternative triage scenarios adjusted for compliance to follow-up.

Figure 31 shows a gain in sensitivity (+10-15%) for CIN2 by repeating cytology (at ASC-US+) at a subsequent triage visit at 6-12 months, whereas the loss in specificity is limited. Adding HPV1618 genotyping to reflex cytology triage yields a small gain in average sensitivity for a considerable loss in specificity.

The reader must be warned that these estimates are very rough.

Figure 31 – Sensitivity and specificity of three scenarios to triage hrHPV+ women: 1) reflex cytology (ASCUS+) triage (green); 2) reflex cytology (ASCUS+) triage (green) completed with 2nd cytology (ASCUS+) triage if reflex triage was negative; 3) reflex triage with cytology and HPV1618 genotyping. Filled symbols represent average values, other symbols represent values from individual studies



4.3.6 *Relative accuracy of cytology and/or hrHPV-DNA based triage algorithms versus reflex cytology (ASC-US+)*

The relative accuracy of the different triage algorithms were compared with reflex cytology at cut-off ASC-US+.

Data on the triage with combined cytology (ASC-US+) or HPV1618 genotyping, versus cytology (ASC-US+) alone was available in the POBASCAM and ATHENA trial[38, 107] (Figure 32, Figure 33). When either cytology or the HPV1618 genotyping test had to be positive, a significantly higher sensitivity (ratio: 1.32 [95% CI: 1.16-1.51] for CIN2+) but lower specificity (ratio: 0.77 [95% CI: 0.74-0.79] for CIN2+) was observed, compared to cytology testing alone. Results were similar for CIN3+ (sensitivity ratio: 1.33 [95% CI: 1.06-1.68], and specificity ratio: 0.73 [95% CI: 0.66-0.82]).

Four studies allowed comparison of reflex cytology triage at cut-of LSIL+ versus ASC-US+[25, 26, 38, 104, 108] (Figure 32, Figure 33). Using LSIL+ as cut-off resulted in a 16% drop in sensitivity (ratio: 0.84 [95% CI: 0.74-0.95] for CIN2+), but a 22% increase in specificity (ratio: 1.22 [95% CI: 1.12-1.33] for CIN2+).

Figure 32 – Relative sensitivity (left) and specificity (right) of two scenarios compared to reflex cytology at cutoff ASC-US+ to detect CIN2+ in women with a positive hrHPV DNA screening test (restricted to scenarios where a pooling from at least 2 studies was possible)

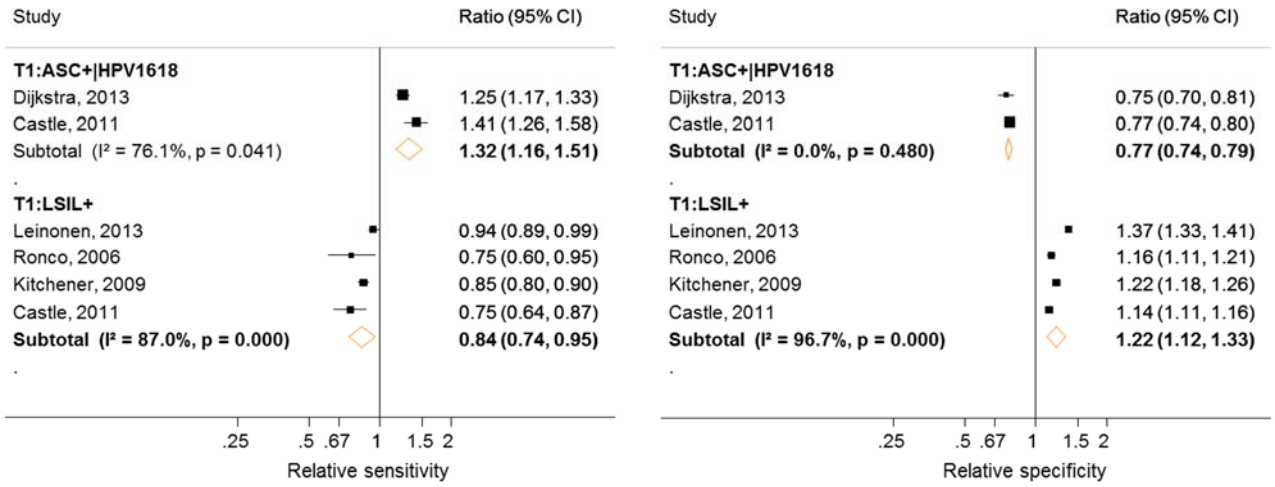
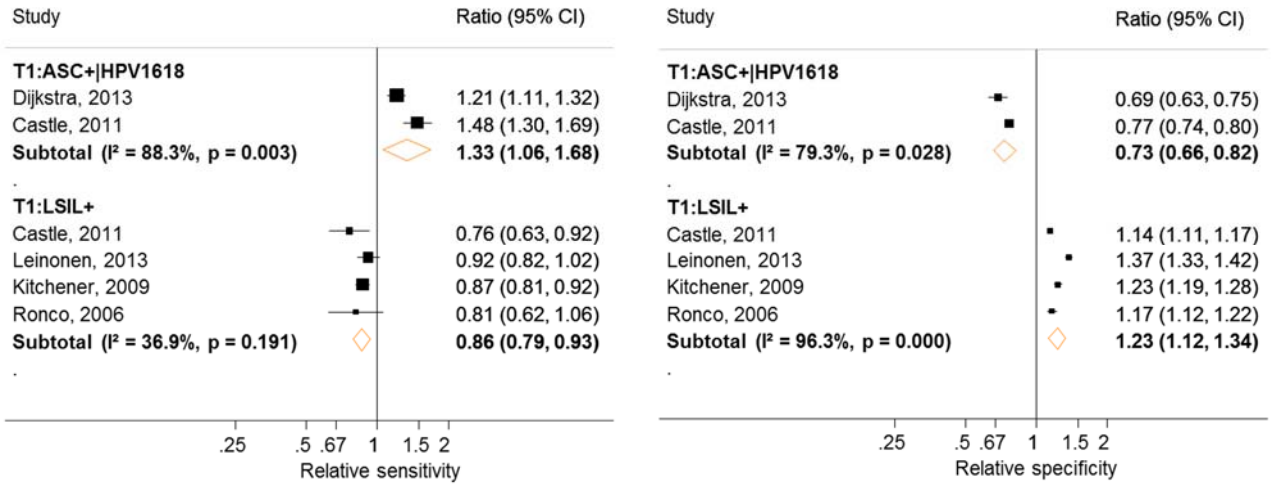


Figure 33 – Relative sensitivity (left) and specificity (right) of two scenarios compared to reflex cytology at cutoff ASC-US+ to detect CIN3+ in women with a positive hrHPV DNA screening test (restricted to scenarios where a pooling from at least 2 studies was possible)



For most triage algorithms, data were available for only one study. Comparisons were separated in two groups containing algorithms with an increased sensitivity (Figure 34, Figure 35) and those with sensitivity loss (Figure 36, Figure 37), compared to reflex cytology at cut-off ASC-US+.

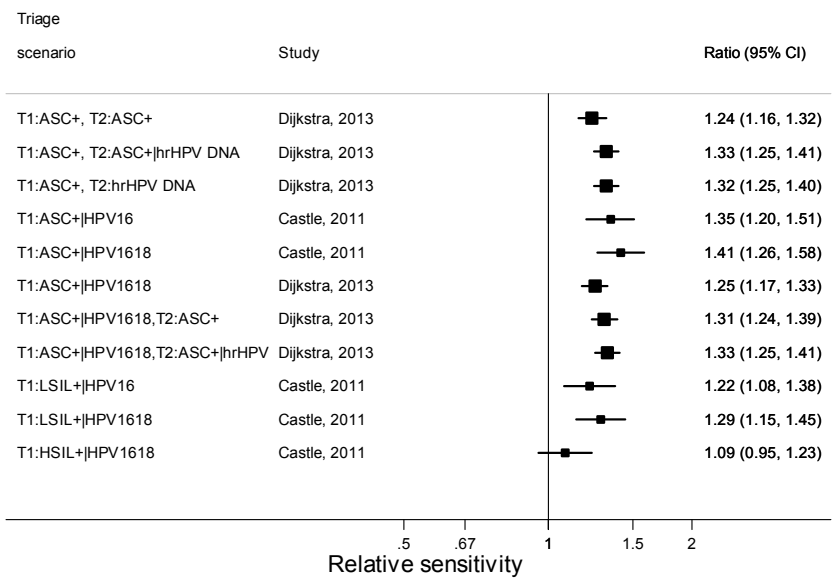
Recalling women with normal reflex cytology for a second triage test with cytology at cut-off ASC-US+ after 6 months (T1:ASC-US+, T2:ASC-US+), resulted in a significantly increased sensitivity (ratio: 1.24 [95% CI: 1.16-1.32] for CIN2+), but a drop in specificity (ratio: 0.91 [95% CI: 0.86-0.96] for CIN2+) in the study of Dijkstra and colleagues[107]. Using a hrHPV-DNA assay in the second triage step further increased sensitivity, but specificity was halved compared to reflex cytology (ASC-US+) alone.

The largest gain in sensitivity was observed when reflex cytology was combined with HPV16 or HPV1618 genotyping and only one of both assays had to be positive (sensitivity ratio: 1.35 [95% CI: 1.20-1.51]and 1.41 [95% CI: 1.26-1.58], respectively)[38]. This however was linked with a significant drop in specificity (ratio: 0.84 [95% CI: 0.82-0.87] and 0.77 [95% CI: 0.74-0.80], respectively).

Reflex triage with HPV1618 genotyping was as sensitive (ratio: 0.99 [95% CI: 0.86-1.13] for CIN2+) and as specific (ratio: 0.99 [95% CI: 0.96-1.02] for CIN2+) as reflex cytology at cut-off ASC-US. Reflex triage with HPV16 genotyping was less sensitive (ratio: 0.84 [95% CI: 0.72-0.97] for CIN2+) but more specific (ratio: 1.09 [95% CI: 1.06-1.12] for CIN2+) compared to reflex cytology.

Triage algorithms using a higher cytology cut-off (LSIL+ or HSIL+) or where both cytology and a genotyping test had to be positive resulted in significantly lower sensitivities compared to reflex cytology.

Figure 34 – Relative sensitivity (left) and specificity (right) of different scenarios compared to reflex cytology at cutoff ASC-US+ to detect CIN2+ in women with a positive hrHPV DNA screening test (restricted to scenarios being more sensitive than the comparator triage test)



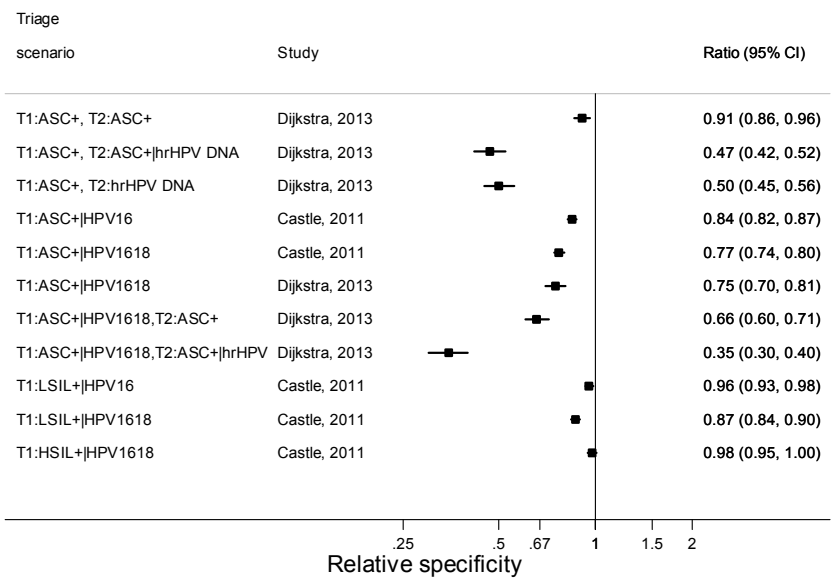


Figure 35 – Relative sensitivity (left) and specificity (right) of different scenarios compared to reflex cytology at cutoff ASC-US+ to detect CIN3+ in women with a positive hrHPV DNA screening test (restricted to scenarios being more sensitive than the comparator triage test)

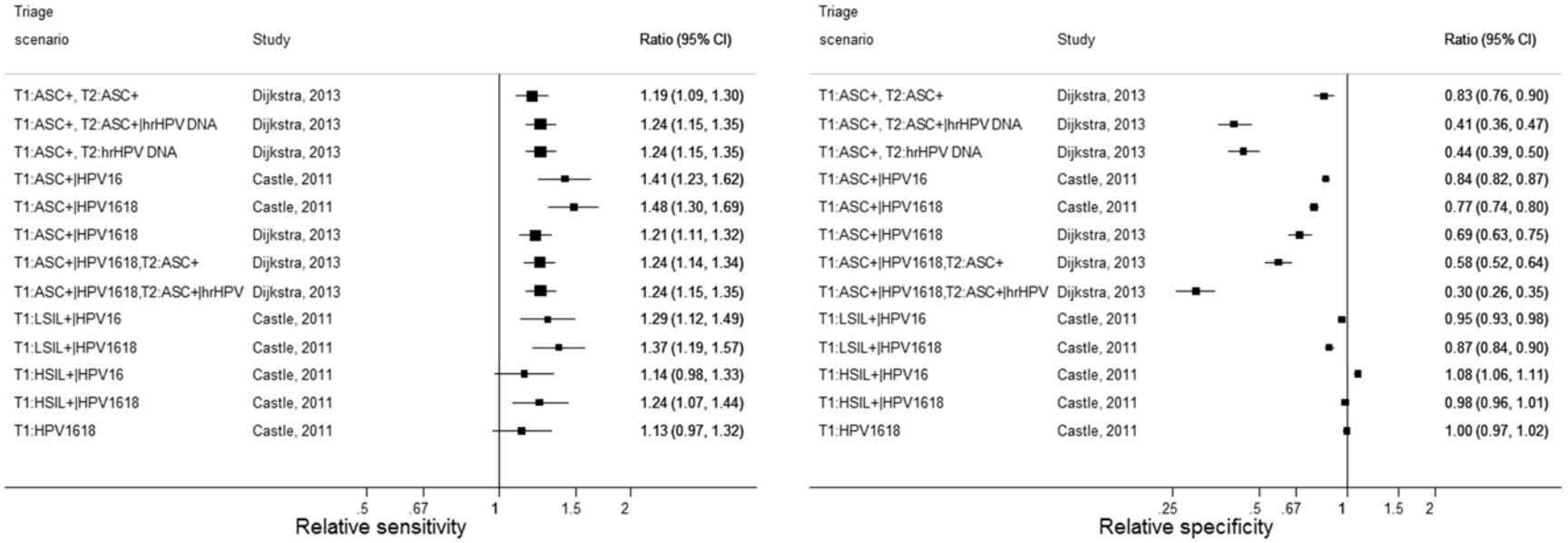


Figure 36 – Relative sensitivity (left) and specificity (right) of different scenarios compared to reflex cytology at cutoff ASC-US+ to detect CIN2+ in women with a positive hrHPV-DNA screening test (restricted to scenarios being less or as sensitive compared to reflex cytology at cutoff ASC-US+)

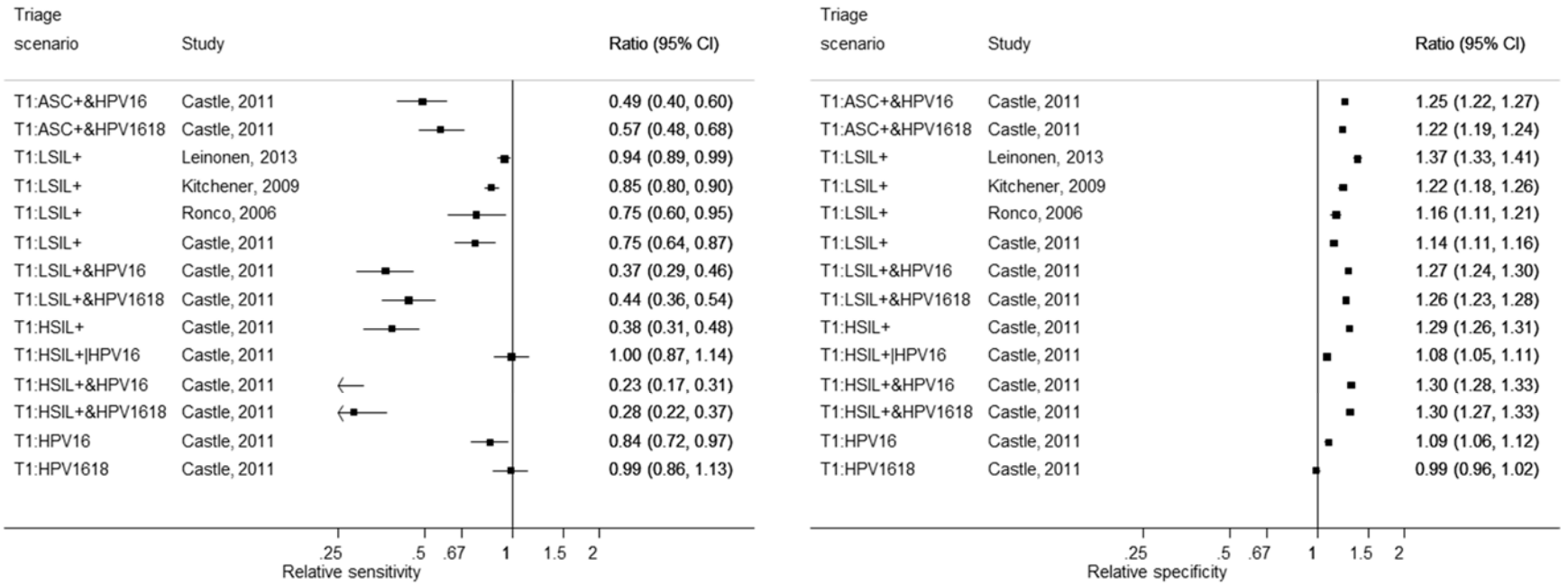
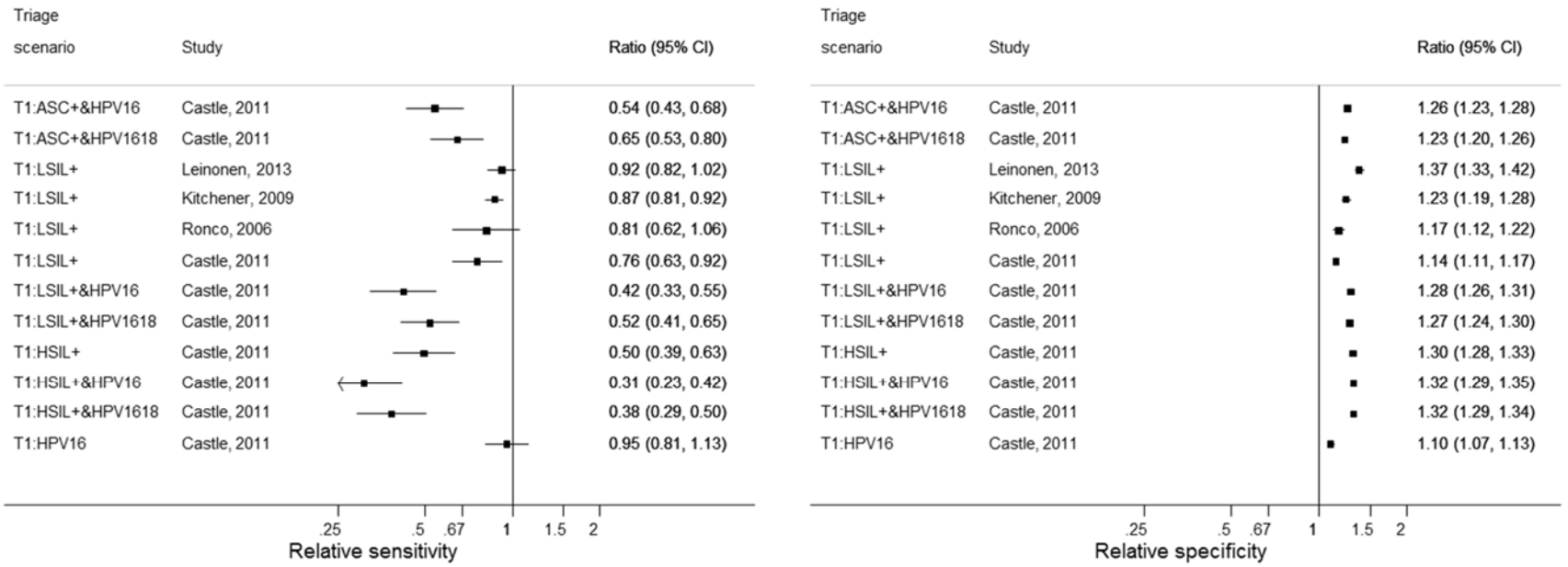


Figure 37 – Relative sensitivity (left) and specificity (right) of different scenarios compared to reflex cytology at cutoff ASC-US+ to detect CIN3+ in women with a positive hrHPV DNA screening test (restricted to scenarios being less or as sensitive compared to reflex cytology at cutoff ASC-US+)



4.3.7 p16^{INK4a} immuno-cytochemistry

One of the seven retrieved RCT's (the phase-2 study of NTCC) contained data on the use of a molecular biomarker (overexpression of p16^{INK4a}) in the triage of hrHPV-positive women. Two reports provided the cross-sectional[105] and longitudinal[106] outcomes of triage based on p16-immunocytochemistry**.** The cross-sectional sensitivity and specificity of reflex triage with p16^{INK4a}, was 88.0% (95% CI: 79.6-93.9) and 60.6% (95% CI: 57.5-63.6%), respectively, for CIN2+, and 90.5% (95% CI: 77.4-97.3%) and 58.4% (95% CI: 55.5-61.4%), respectively, for CIN3+[105] (Table 21).

The longitudinal sensitivity for p16^{INK4a} assessed over three years was lower than the cross-sectional sensitivity regarding detection of CIN2+ (88.0% vs. 79.0%) and CIN3+ (90.5% vs. 84.6%), indicating disease development in women with a negative reflex p16^{INK4a} test[109] (Table 21).

Table 21 – Absolute sensitivity and specificity for reflex p16^{INK4a} triage for women with a positive hrHPV test

Study		Test (cut-off)	Outcome	Absolute accuracy	
				Sensitivity (95% CI)	Specificity (95% CI)
Carozzi 2008	Cross-sectional	p16INK4a (1 stained cell)*	CIN2+	88.0% (79.6-93.9)	60.6% (57.5-63.6)
Carozzi 2008	Cross-sectional	p16INK4a (1 stained cell)*	CIN3+	90.5% (77.4-97.3)	58.4% (55.5-61.4)
Carozzi 2013	Longitudinal§	p16INK4a (1 stained cell)	CIN2+	79.0% (71.4-85.4)	62.6% (59.0-66.0)
Carozzi 2013	Longitudinal§	p16INK4a (1 stained cell)	CIN3+	84.6% (73.5-92.4)	59.1% (55.6-62.4)

** The cut-off with the best sensitivity. § Cumulative disease after three years of follow-up.*

By lack of an intra-study comparator, no relative accuracy could be derived for p16-based triage in NTCC-2. However, by comparing with absolute accuracy measures for ASC-US+ triage from NTCC-1 (cross-sectional sensitivity of 75.3% [95% CI: 64.5-84.2] for CIN2+, 82.1% [95% CI: 66.5-92.5%] for CIN3+; specificity of 75.8% [95% CI: 73.1-78.3%] for CIN2+, 74.1% [95% CI: 71.5-76.6%]), we may also obtain credible relative accuracy. Allowing for this inter-NTCC comparison, we can conclude that p16-based triage was 1.17 times (95% CI: 1.01-1.35) more sensitive to detect CIN2+ and 1.10 times (95% CI: 0.92-1.32) to detect CIN3+ compared to simple cytology triage at cut-off ASC-US. The specificity of p16 triage was significantly lower than ASC-US+ triage: ratio of 0.80 (95% CI: 0.75-0.85) and 0.79 (95% CI: 0.74-0.84), considering outcomes CIN2+ and CIN3+, respectively.

Using p16^{INK4a}/Ki-67 detection to manage hrHPV-positive/cytology-negative women

Another study was identified containing data on triage with p16^{INK4a}/Ki-67 double staining of women who were hrHPV-positive but had normal cytology at primary screening[110].

In this study the p16^{INK4a}/Ki-67 triage had a sensitivity and specificity of 91.9% (95% CI: 78.1-98.3) and 80.9% (95% CI: 76.7-84.7) for CIN2+. To detect CIN3+, triage with p16^{INK4a}/Ki-67 resulted in a sensitivity and specificity of 96.4% (95% CI: 81.7-99.9) and 79.6% (95% CI: 75.3-83.5).

4.4 Risk of CIN3+ in hrHPV-positive women with positive or negative triage test results

Sensitivity and specificity are test characteristics reflecting the capacity to identify diseased subjects by a positive test result and non-diseased subjects by a negative test result. These are test characteristics which are typically not influenced by disease prevalence. Therefore, in systematic reviews and meta-analyses, sensitivity and specificity are the test measures that are pooled to synthesize knowledge on test performance.

However, patients, clinicians, and decision makers defining policies for good clinical practice, are in the first place interested in the probability of disease when a test is positive (positive predictive value: PPV) and the risk of disease when a test is negative (complement of the negative predictive value: 1-NPV=cNPN). The PPV provides information on the risk of underlying pre-cancer and consequently on the efficiency of referral for further management. The inverse of the PPV (1/PPV) corresponds with the number needed to refer [colposcopy/biopsy] to find 1 case of cervical pre-cancer. The NPV provides assurance on the safety that a women does not have (pre)-cancer and will have a very low risk to develop (pre-)cancer by the next screening round.

Below, we computed the predictive values for a plausible series of background risks of CIN3+ (possible pretest probabilities) which are relevant for the settings where the evaluated tests will possibly be used. The

predictive values, computed for a given setting/area, allow decision making regarding the use of a test in this setting/area. The risk of underlying pre-cancer or cancer (CIN3+) should be sufficiently low in case of a negative screen test result to reassure women and to refer them back to the normal screening schedule[111]. Whereas the risk of CIN3+ should be sufficiently high if the screening test is positive (=PPV). If the PPV is not high enough a triage test is needed.

We considered the following range of background risks of cervical pre-cancer or cancer among women with a positive hrHPV DNA test at screening:

- Low: 5%
- Intermediate: 9% (corresponding to the average cumulative risk of CIN3+ among hrHPV DNA+ women)
- High: 15%.

The low and high estimates correspond with rounded low and high risks observed in the aforementioned screening trials.

We accepted the following cutoffs for the measures of efficiency (PPV) and safety (cNPV), considering prevalent CIN3+ as targeted prevalent disease:

- PPV: >10%
- cNPV: <1%.

In addition, the following cut-offs for longitudinal PPV and cNPV over a period of five years after the screening test were accepted.

- PPV_{long}: >20%
- $cNPV_{long}$: <1%.

The risk or post-test probability of CIN3+ after a positive or negative result of a given triage scenario was computed from:

1. absolute accuracy of the reference triage (reflex cytology at ASC-US+);
2. relative accuracy of the given scenario estimated using a binormal model;
3. assumed underlying low, intermediate and high-risk of CIN3+.

The results are shown in Table 22.

In nearly all triage scenario's and back ground risk situations, more than 10% of triage-positive women will have or will develop CIN3+. Exceptions are some very sensitive two-step triage scenarios (3,4,9 & 10) in low-risk situations (T1:ASC-US+, T2:ASC-US+ | hrHPV; T1:ASC-US+, T2:hrHPV; T1:ASC-US+|HPV1618, T2:ASC-US+; T1:ASC-US+|HPV1619, T2:ASC-US+ | hrHPV).

All two-step scenarios, in low and intermediate risk situations, resulted in a post-test probability <1% when the triage test is negative. In a low-risk situation, also negative reflex-cytology combined with negative HPV1618 genotyping or a negative p16 test is accompanied with <1% post-test probabilities.

In a high-risk situation only two-step triage scenarios (3,4,9 & 10) are associated with <1% post-test probabilities. These last four scenarios are the only which are both efficient (PPV>10%) and safe (cNPV<1%).

In a low-risk situation, two-step triage with reflex-cytology at baseline and at 6-12 months later looks a good triage method (both triage criteria fulfilled, outcome documented over >=36 months and referral rate to colposcopy of only 39%). However, loss to follow-up should be taken into account when triage involves more visits. Avoiding the necessity for repeat testing reduces the risk of loss to follow-up. In the two Dutch trials, the compliance with follow-up after six and twelve months was ~60% and ~75%, repectivey[28, 112]. Other studies have also demonstrated considerable loss to follow-up at repeat testing, particularly after normal cytology. Therefore more sensitive one step reflex-triage scenarios are interesting as well, such as T1: ASC-US+ combined with HPV1618 genotyping, which results always in an good PPV (≥10%) in low- and intermediate risk situation and an acceptable cNPV in low- risk situation.

Table 22 – Number of true and false-positives among 1000 women with a positive hrHPV test at screening and triaged with one of 23 different scenarios, positive predictive value (PPV=risk of CIN3+ if triage-positive), 1/PPV (number needed to refer to find 1 case of CIN3+), negative predictive value (NPV) and the complement of NPV (cNPV=1-NPV=risk of CIN3+ if triage-negative) estimated for three situations of underlying background risk of CIN3+ (risk=5%, 9% and 15%)

	Triage1	Triage2	Background risk	Sensitivity	Specificity	Useful referrals	Missed cases	Unnecessary referrals	True reassurance						Criteria fulfilled
						TP	FN	FP	TN	PPV	1/PPV	NPV	cNPV	test+	
1	ASC-US+		0.05	0.81	0.71	40	10	277	673	0.13	7.93	0.99	0.015	0.32	
2	ASC-US+	ASC-US+	0.05	0.95	0.64	47	3	340	610	0.12	8.23	1.00	0.005	0.39	x
3	ASC-US+	ASC-US+ | hrHPV	0.05	1.00	0.35	50	0	622	328	0.07	13.44	1.00	0.000	0.67	
4	ASC-US+	hrHPV	0.05	1.00	0.37	50	0	601	349	0.08	13.02	1.00	0.000	0.65	
5	ASC-US+|HPV16		0.05	0.91	0.58	46	4	399	551	0.10	9.67	0.99	0.007	0.45	x
6	ASC-US+&HPV16		0.05	0.59	0.93	30	20	65	885	0.32	3.17	0.98	0.022	0.10	
7	ASC-US+|HPV1618		0.05	0.93	0.53	47	3	445	505	0.10	10.47	0.99	0.006	0.49	x
8	ASC-US+&HPV1618		0.05	0.66	0.91	33	17	85	865	0.28	3.58	0.98	0.019	0.12	
9	ASC-US+|HPV1618	ASC-US+	0.05	0.99	0.44	50	0	530	420	0.09	11.60	1.00	0.000	0.58	
10	ASC-US+|HPV1618	ASC-US+ | hrHPV	0.05	1.00	0.24	50	0	724	226	0.06	15.48	1.00	0.000	0.77	
11	LSIL+		0.05	0.71	0.85	36	14	142	808	0.20	4.94	0.98	0.017	0.18	
12	LSIL+ | HPV16		0.05	0.89	0.68	44	6	302	648	0.13	7.86	0.99	0.009	0.35	x
13	LSIL+ & HPV16		0.05	0.51	0.96	26	24	37	913	0.41	2.42	0.97	0.026	0.06	
14	LSIL+ | HPV1618		0.05	0.91	0.61	45	5	369	581	0.11	9.20	0.99	0.009	0.41	x
15	LSIL+ & HPV1618		0.05	0.58	0.95	29	21	49	901	0.37	2.69	0.98	0.023	0.08	
16	HSIL+		0.05	0.56	0.98	28	22	24	926	0.54	1.86	0.98	0.023	0.05	
17	HSIL+ | HPV16		0.05	0.85	0.78	42	8	210	740	0.17	6.00	0.99	0.011	0.25	
18	HSIL+ & HPV16		0.05	0.41	0.99	21	29	10	940	0.68	1.48	0.97	0.030	0.03	
19	HSIL+ | HPV1618		0.05	0.87	0.69	44	6	291	659	0.13	7.61	0.99	0.009	0.34	x
20	HSIL+ & HPV1618		0.05	0.48	0.99	24	26	12	938	0.67	1.50	0.97	0.027	0.04	

21	HPV16		0.05	0.79	0.79	39	11	198	752	0.16	6.08	0.99	0.014	0.24	
22	HPV1618		0.05	0.84	0.70	42	8	280	670	0.13	7.67	0.99	0.012	0.32	
23	p16		0.05	0.89	0.56	44	6	418	532	0.10	10.50	0.99	0.011	0.46	x
1	ASC-US+		0.09	0.81	0.71	75	18	264	643	0.22	4.52	0.97	0.027	0.34	
2	ASC-US+	ASC-US+	0.09	0.95	0.64	88	5	325	582	0.21	4.69	0.99	0.009	0.41	x
3	ASC-US+	ASC-US+ | hrHPV	0.09	1.00	0.35	93	0	594	313	0.14	7.39	1.00	0.000	0.69	x
4	ASC-US+	hrHPV	0.09	1.00	0.37	93	0	573	334	0.14	7.16	1.00	0.000	0.67	x
5	ASC-US+|HPV16		0.09	0.91	0.58	85	8	381	526	0.18	5.48	0.99	0.015	0.47	
6	ASC-US+&HPV16		0.09	0.59	0.93	55	38	62	845	0.47	2.13	0.96	0.043	0.12	
7	ASC-US+|HPV1618		0.09	0.93	0.53	87	6	425	482	0.17	5.89	0.99	0.012	0.51	
8	ASC-US+&HPV1618		0.09	0.66	0.91	61	32	81	826	0.43	2.33	0.96	0.037	0.14	
9	ASC-US+|HPV1618	ASC-US+	0.09	0.99	0.44	92	1	506	401	0.15	6.50	1.00	0.002	0.60	x
10	ASC-US+|HPV1618	ASC-US+ | hrHPV	0.09	1.00	0.24	93	0	691	216	0.12	8.43	1.00	0.000	0.78	x
11	LSIL+		0.09	0.71	0.85	66	27	136	771	0.33	3.06	0.97	0.034	0.20	
12	LSIL+ | HPV16		0.09	0.89	0.68	83	10	289	618	0.22	4.48	0.98	0.016	0.37	
13	LSIL+ & HPV16		0.09	0.51	0.96	48	45	36	871	0.57	1.75	0.95	0.049	0.08	
14	LSIL+ | HPV1618		0.09	0.91	0.61	84	9	353	554	0.19	5.20	0.98	0.016	0.44	
15	LSIL+ & HPV1618		0.09	0.58	0.95	54	39	47	860	0.53	1.87	0.96	0.043	0.10	
16	HSIL+		0.09	0.56	0.98	52	41	22	885	0.70	1.42	0.96	0.044	0.07	
17	HSIL+ | HPV16		0.09	0.85	0.78	79	14	200	707	0.28	3.53	0.98	0.019	0.28	
18	HSIL+ & HPV16		0.09	0.41	0.99	38	55	10	897	0.79	1.26	0.94	0.058	0.05	
19	HSIL+ | HPV1618		0.09	0.87	0.69	81	12	277	630	0.23	4.42	0.98	0.019	0.36	
20	HSIL+ & HPV1618		0.09	0.48	0.99	44	49	11	896	0.80	1.25	0.95	0.052	0.06	
21	HPV16		0.09	0.79	0.79	73	20	189	718	0.28	3.59	0.97	0.027	0.26	
22	HPV1618		0.09	0.84	0.70	78	15	268	639	0.23	4.44	0.98	0.023	0.35	
23	p16		0.09	0.89	0.56	80	10	400	510	0.17	6.00	0.98	0.019	0.48	

1	ASC-US+		0.15	0.81	0.71	121	29	248	602	0.33	3.05	0.95	0.046	0.37	
2	ASC-US+	ASC-US+	0.15	0.95	0.64	142	8	304	546	0.32	3.14	0.99	0.014	0.45	
3	ASC-US+	ASC-US+ | hrHPV	0.15	1.00	0.35	150	0	556	294	0.21	4.71	1.00	0.000	0.71	x
4	ASC-US+	hrHPV	0.15	1.00	0.37	150	0	537	313	0.22	4.58	1.00	0.000	0.69	x
5	ASC-US+|HPV16		0.15	0.91	0.58	137	13	357	493	0.28	3.61	0.97	0.026	0.49	
6	ASC-US+&HPV16		0.15	0.59	0.93	89	61	58	792	0.61	1.65	0.93	0.072	0.15	
7	ASC-US+|HPV1618		0.15	0.93	0.53	140	10	398	452	0.26	3.84	0.98	0.022	0.54	
8	ASC-US+&HPV1618		0.15	0.66	0.91	98	52	76	774	0.56	1.78	0.94	0.063	0.17	
9	ASC-US+|HPV1618	ASC-US+	0.15	0.99	0.44	149	1	475	375	0.24	4.19	1.00	0.003	0.62	x
10	ASC-US+|HPV1618	ASC-US+ | hrHPV	0.15	1.00	0.24	150	0	647	203	0.19	5.31	1.00	0.000	0.80	x
11	LSIL+		0.15	0.71	0.85	107	43	127	723	0.46	2.19	0.94	0.056	0.23	
12	LSIL+ | HPV16		0.15	0.89	0.68	133	17	271	579	0.33	3.04	0.97	0.029	0.40	
13	LSIL+ & HPV16		0.15	0.51	0.96	77	73	33	817	0.70	1.43	0.92	0.082	0.11	
14	LSIL+ | HPV1618		0.15	0.91	0.61	136	14	330	520	0.29	3.43	0.97	0.026	0.47	
15	LSIL+ & HPV1618		0.15	0.58	0.95	87	63	44	806	0.66	1.51	0.93	0.072	0.13	
16	HSIL+		0.15	0.56	0.98	84	66	21	829	0.80	1.25	0.93	0.074	0.11	
17	HSIL+ | HPV16		0.15	0.85	0.78	127	23	188	662	0.40	2.48	0.97	0.034	0.32	
18	HSIL+ & HPV16		0.15	0.41	0.99	62	88	9	841	0.87	1.15	0.91	0.095	0.07	
19	HSIL+ | HPV1618		0.15	0.87	0.69	131	19	260	590	0.34	2.98	0.97	0.031	0.39	
20	HSIL+ & HPV1618		0.15	0.48	0.99	72	78	11	839	0.87	1.15	0.91	0.085	0.08	
21	HPV16		0.15	0.79	0.79	118	32	177	673	0.40	2.50	0.95	0.045	0.30	
22	HPV1618		0.15	0.84	0.70	126	24	251	599	0.33	2.99	0.96	0.039	0.38	
23	p16		0.15	0.89	0.56	133	17	374	476	0.26	3.81	0.97	0.034	0.51	

4.5 Discussion

In the near future, screening for cervical cancer will likely shift from cytological to virological screening. However, the optimal management of women with a hrHPV infection remains an imperative issue to solve, since hrHPV testing has a lower cross-sectional specificity compared to cytology[6]. As a consequence, the triage of hrHPV positive women is needed to limit the burden of follow-up and to avoid over-diagnosis and over-treatment as much as possible.

Different triage options nested in large screening trials using an hrHPV assay as a primary screening test, enabled us to assess the accuracy of diverse strategies to manage hrHPV-positive women.

A two-step triage scenario with twice cytology at cutoff ASC-US+ (strategy 2 in Table 22) offers a good balance of efficiency (4 to 9 referrals to detect one CIN3+, ~40% of referral) and safety (risk of CIN3+ in triage-negative women of 0.5% to 0.9%). If the background risk is higher (>=15%), the safety becomes borderline (risk of CIN3+ in next 3-5 years of 1.4%). In the Netherlands, this scenario has been chosen for the future HPV-based screening policy, which will be applied the whole country in 2016. The safety of strategy 2 can be increased by adding HPV16 or HPV1618 genotyping and/or hrHPV testing, or by replacing cytology with a repeat hrHPV test. In these scenarios, safety criteria are obviously fulfilled, even when the background risk is high, but they are accompanied by a substantially increased referral rate (67% to 71%).

Two-step scenarios are characterised by a certain degree of drop-out of women under follow-up. Where this drop-out is important, more sensitive reflex triage scenarios could be favoured which involve reflex cytology combined with HPV1618 genotyping (scenarios 7 and 14). However, these scenarios do not reach the safety criterion when the back ground risk is intermediate or high.

Limits and strengths of the review

Because of time constraints the current review was restricted to large population-based trials comparing HPV-based with cytology-based screening. A more comprehensive literature review is currently being done. However, it is expected that the main bulk of useful information on triage of HPV+ women may be included in the studies retrieved in this review.

Timing of outcome is often limited to a few months after observation of the hrHPV screen test result. Outcomes from studies comprising up to 3-4 years of surveillance provide more useful information (see Table 17) than those with only 3-6 months of follow-up. Unfortunately, no results were available for 5 years of follow-up or more.

Many scenarios of triage are documented in few and often even in only one study. Moreover, the inter-study heterogeneity in the absolute accuracy values observed in multiple studies assessing a particular scenario, often was large. However, by assessing the relative accuracy, variability was reduced and therefore, absolute accuracies predicting the outcomes were based on the product of the accuracy of the reference triage scenario (reflex cytology at ASC-US documented in eight reports) * relative accuracy of a given scenario compared with this reference.

Not all relevant triage information reported in secondary publications of the screening trials could be included in a formal meta-analysis since only proportions or rates were reported with different assumptions applied for adjustment for follow-up compliance. Adjustment for incomplete compliance could not be assessed statistically since it requires availability of the absolute data. Requesting data from authors will be done within COCEAHR, but cannot yet be included in the current review.

The definition of criteria for good triage scenario's (PPV>10% and cNPV<1%, considering CIN3+ as outcome) are arbitrary and depend on length of duration of follow-up. The choice was based on conventions agreed among certain experts. International consensus building on these criteria may be needed and should involve policy makers, clinical experts, systematic reviewers, health economists and patient organisations. Criteria for the outcome cancer may be preferred but these criteria would today not be verifiable. Nevertheless, incidence of invasive cancer according to triage policy and compliance with this policy should be target of monitoring based in systematic linkages with screening and cancer registries.

The future evaluation of multiple step triage scenarios should include the proportion of CIN3+ identified at each successive step beyond the baseline step and the proportion of drop-out at each additional follow-up visit in order to assess to overall cumulative sensitivity and safety compared to one-step scenarios.

Other markers may be useful in triage of hrHPV-positive women as well (in particular, double immune-staining for p16 and Ki67, hypermethylation profiles, expression of oncoproteins such as E6 and E7, chromosomal aberrations, viral mRNA testing, evolution of type specific viral load) and may provide alternatives for the triage scenarios considered in this review. Some publications are expected to become available in the near future and should be included in updated reviews as soon as possible.

In the current review, triage with reflex cytology and repeat cytology appeared to be an acceptable scenario. However, it should be mentioned that the quality of cytology in the field may be more heterogeneous than in the trials included in this review. Triage with objective bio-markers could reduce this variability.

5 QUALITY CONTROL SYSTEMS

5.1 Quality control systems in HPV testing

5.1.1 Interpretation of the WHO HPV Laboratory Manual 2009 towards Belgian application

The WHO HPV Laboratory Manual[113] was developed by the WHO HPV LabNet (Laboratory Network) and aims to assist in establishing the laboratory support required for effective monitoring of HPV vaccination programmes. Vaccination is directed towards prevention of HPV infection, but the public-health outcome of interest is cervical cancer. Current uses of HPV testing in screening and clinical diagnosis are directed towards detection of HPV-associated precancers that are treated, rather than to detect HPV infection per se. Moreover, HPV tests in clinical use often do not provide type-specific information. This limits the usefulness of data from clinical HPV testing in HPV epidemiology and surveillance. To produce HPV data that can be compared and interpreted worldwide, IS (international standards) and standardized procedures for HPV test performance are required.

5.1.2 Laboratory quality assurance

HPV tests required for documenting type-specific prevalence and monitoring the impact of vaccination are different from clinical tests, in that they should have optimal analytic (rather than clinical) sensitivity and specificity. Similarly, the high sensitivity HPV tests (e.g. PCR) needed in epidemiology and vaccinology may not be optimal for clinical HPV testing. The ideal assays should have: 1) good sensitivity and specificity as evaluated in international proficiency testing; 2) ease of transfer to laboratories with varying levels of experience and resources; 3) ‘affordable’ cost, to allow use in low-resource settings.

There are a variety of HPV tests in use worldwide and several of these may be appropriate to use for HPV surveillance and HPV vaccine impact monitoring (see Poljak 2012 for an overview[20]). Options for measures of HPV and immune response to vaccination include DNA detection and serology (the detection of specific antibodies in serum).

Results of HPV testing are greatly impacted by the assay and therefore, all steps of HPV detection and typing used by a global network need careful standardization. Setting up a quality assurance system in a laboratory ensures the proper planning of activities and the provision of adequate resources to implement them. It promotes full and accurate reporting and provides the tools to verify the integrity of activities. It is the responsibility of the head of the laboratory to establish, implement and ensure compliance with laboratory quality assurance. However, laboratory quality assurance is the responsibility of all laboratory personnel.

5.1.3 Current situation in Belgian laboratories

In Belgium, an ISO15189 accreditation (including participation in external quality assessments) for high-risk HPV detection in cervicovaginal samples using a molecular method - but not for cytopathology - is mandatory for reimbursement. This International Standard specifies the quality requirements and competence that are particular for medical laboratories. A medical laboratory's fulfillment of the requirements of this International Standard means the laboratory meets both the technical competence requirements and the management system requirements that are necessary for it to consistently deliver technically valid results.

The Scientific Institute of Public Health organises an external control procedure for HPV DNA testing via QCMD. Samples are prepared from cell cultures infected with HPV and fixed in PreservCyt (ThinPrep, Hologic). Belgian laboratories requesting reimbursement for bio-molecular testing for HPV must have an ISO15189 accreditation and participate in an external quality control programme. In 2013, 44 Belgian laboratories participated in this QC programme.

5.1.3.1 Collection and handling of specimens for HPV testing

Serology

Standard methods for collection of peripheral blood and serum are required for HPV serology.

Cervical cells

HPV is a cell-associated virus, and an adequate cellular sample with preserved DNA from the site of infection is required. Different methods of sample collection and handling can influence the final result. Methods of sampling vary in their cost and ease of implementation. Laboratories should apply them consistently to provide reliable results. Collection method, media and processing prior to HPV testing must be matched to the method of testing and to cytology. Specimens must be shipped and stored under conditions that protect sample integrity for testing.

European guidelines exist for the collection and preparation of cellular specimen for cyto-pathological specimen.[114] The left-over of currently used liquid-based cytology methods remnant after cytological interpretation can also be used for HPV DNA detection. Special requirements may be needed for HPV RNA detection. Manufacturers of HPV assays, usually provide recommendations or kits for collection and transport media.

5.1.3.2 Assay validation

Laboratories must validate the assay they use for the detection of HPV DNA with the specified samples. Validation is the process of establishing documented evidence to provide a high degree of assurance that a procedure will consistently perform as intended. Established methods, e.g. commercial assay kits which are FDA approved, have undergone validation. When such tests are used, each laboratory needs to verify performance and demonstrate suitability for its purpose under actual conditions of use in the individual laboratory concerned. In-house tests need full validation. Parameters to be examined will depend on whether the assay is qualitative or quantitative.

The Hybrid Capture 2 assay and the GP5+/6+ PCR are two hr-HPV DNA assays that are considered as clinically validated for cervical cancer screening. Indeed, randomised trials have proven that their use results in lower incidence of CIN3+ and cancer observed in the 2nd screening round compared to screening with cytology (see 1.1)[6]. Requirements in terms of non-inferior sensitivity and specificity for CIN2+ compared to Hybrid Capture 2 assay and GP5+/6+ PCR and minimal intra- and inter-laboratory reproducibility have been defined for use of new HPV DNA assays in primary cervical cancer screening[44]. A list of clinically validated HPV assays that fulfil

these requirement was published recently[6]. Currently the following HPV DNA tests can be considered as clinically validated according the Meijer guideline: Abbott RT hr HPV test, COBAS-4800, Papillocheck, and two PCR assays targeting (E6/E7) of separate high-risk HPV types. However, the list is changing rapidly and an updated list should be consulted.

5.1.3.3 External quality assessment

Participation in external quality assessment (proficiency testing and/or confirmatory testing) allows laboratories to verify that they have successfully implemented HPV detection and typing assays. Results allow an evaluation of individual laboratory performances, as well as an evaluation of whether assay platforms used by multiple laboratories are robust in terms of the generation of acceptable results in many laboratories (assay characteristics).

5.1.3.4 Data management

An essential part of the work of the laboratory is to record the details of all specimens tested, to record the results of testing and to report the results. Good laboratory data management is crucial for monitoring the impact of HPV vaccination through HPV testing. It is highly desirable that all laboratories establish a computer-record system or an electronic data-management system. Which information is reported, where it is reported from and where it is reported to, must be clearly agreed upon by all parties involved in the system.

5.1.3.5 Forms of quality control

The proficiency testing organized by WHO Network of HPV reference labs evaluates analytical accuracy of HPV testing in a given laboratory with a given test and can be considered as a kind of external quality control. Reaching a high level for this type of proficiency is an important condition for surveillance of HPV vaccination effects.

This type of quality control may be less relevant for screening for cervical cancer where the purpose is to detect progressive cervical neoplastic lesions and finding transient infections has to be considered as false-positive results. Linkage of HPV screen test results with cytopathology and cancer registry data is from a public health point of view a more appropriate form of quality control.

It might be obvious that general good laboratory practice guidelines established in a quality handbook should also be in place for virological laboratories.

Service to clients (health authorities, clinicians, patients) should also be subject of quality control and can involve delivery of sampling and storage material, turn-over time (time span between collection – arrival – testing of samples and reporting of results); data collection and communication with other databases for reasons of programme evaluation are other elements.

5.1.4 Role of a national HPV reference laboratory

Reference laboratory networks have played an instrumental role in the control of major epidemics and endemics such as influenza, measles, polio, hepatitis and other vaccine preventable diseases. In the framework of the introduction of prophylactic HPV vaccination, experts at the level of the World Health Organisation have defined the rational for setting up a network of reference laboratories dedicated to testing for nucleic acids of and antibodies against human papillomaviruses. The purpose was to facilitate the implementation of validated, standardized laboratory procedures; by developing quality assurance and proficiency testing; by training personnel and supplying equipment if required; and by providing a network for surveillance.[115] The network's mission would be to contribute to improving quality of laboratory services for effective surveillance and HPV vaccination impact monitoring, through enhanced, state-of-the-art laboratory support. An additional task is the development of international standard materials which facilitate inter-laboratory comparisons and improves laboratory performance. An international standard is a preparation to which an international unit (IU) of activity has been assigned. The Global laboratory has in the meanwhile standard preparations of given amounts of plasmids containing HPV full genomic cDNA sequences. Standards are also developed for anti HPV serology.

The Network has developed proficiency panels consisting in coded samples composed of purified plasmids of different calibrated compositions and concentrations of HPV genotypes, which are distributed to laboratories performing HPV testing with their own particular assay.

Laboratories identifying correctly 50 international units (IU) of HPV16 and HPV18 and 500 IU of other high-risk HPV genotypes are considered

proficient. Successive proficiency studies have demonstrated improved proficiency among participating laboratories.[116, 117]

The Network is conceptualised hierarchically with one Global WHO reference lab (currently based in Stockholm), a series of continental reference laboratories (one in each WHO Region) which coordinate a network of country-based reference laboratories[116, 117].

The following European countries have a national HPV reference laboratory: Czech Republic, Denmark, England, France, Germany, Italy, Norway, Scotland, Slovenia, Switzerland, Sweden.

Contacts have been established with the Scottish and French laboratories, via: Prof. K. Cuschieri (Edinburgh) and Dr. I. Heard & Dr. M. Favre (Institut Pasteur, Paris):

- Centre National de Référence pour les Papillomavirus (CNR-HPV) (http://www.pasteur.fr/ip/easysite/go/03b-000031-00a/identite-et-coordonnees)
- The Scottish Human Papillomavirus Reference Laboratory (SHPVRL) (http://www.hps.scot.nhs.uk/reflab/VirLabDetail.aspx?id=26)

From the discussion with the directors of these laboratories, the consultation of their websites and from the terms of references described in the aforementioned WHO references, a list of tasks for a Belgian reference laboratory have been defined (see following section).

For approximately fifty pathogenic infectious agents, reference centres exist in Belgium, but HPV is not yet included in the list. Because of the limited number of tests used for currently recognised clinical indications of HPV testing (triage of ASC-US and follow-up after treatment of cervical precancer), the need for a reference laboratory was not expressed up hereto. However, given the introduction of prophylactic HPV vaccination, the expected introduction of HPV-based screening, and WHO recommendation, the committee of experts in microbiology recently expressed the need to create such reference centre dedicated to human papillomaviruses.

Besides the generic tasks foreseen for all Reference Centres for human microbiology, the Belgian HPV Reference Laboratory should fulfil the following specific tasks:

- To provide testing services (identifying DNA or RNA of HPV genotypes) to evaluate the impact of the HPV immunisation programme on the incidence and prevalence of HPV related disease and HPV infection in the Belgian population).
- To assess, in collaboration with existing competent services, the distribution of HPV genotypes by testing targeted series of archived residual cytological specimen collected in the framework of cervical cancer screening.
- To provide information of the use do international standard reagents for HPV DNA and antibody detection.
- To contribute to and collaborate in European networks aiming to evaluate different combinations of HPV screening and HPV vaccination.
- To validate HPV assays (detecting nucleic acids of high-risk types as group test, of individual HPV genotypes) and/or to contribute in validation of assays in collaboration with the international networks of HPV reference laboratories and to organize a forum for decision making on HPV assays that can be used in clinical practice or for epidemiological surveillance.
- To define the list of HPV tests which can be used for screening and management of screen-positive subjects. To advice authorities in the principles of selection of tests and devices which can be used in clinical practice based on test performance, cost-effectiveness and logistics.
- To set up expertise of HPV testing of other than clinical cervical cell samples (self-collected specimen, other ano-genital specimen, oral, pharyngeal samples and samples from other anatomical localisations).
- To advice and inform health authorities on use of HPV testing in Belgium.
- To provide a service of proficiency of HPV testing in Belgian laboratories in collaboration with: the Dienst Kwaliteit van medische laboratoria | Service Qualité des laboratoires médicaux (Operationele Directie Expertise, dienstverlening en klantenrelaties | Direction Opérationelle Expertise, prestations de service et relations clients) of the Scientific Institute of Public Health ; and the Regional WHO HPV reference laboratory (currently based in Lausanne, Switzerland for the European WHO area).

- To contribute in setting up a quality control and quality assurance system with respect to the use of HPV testing in cervical cancer screening and management of screen-positive women. The contribution in quality assurance with respect to the cyto-pathological examinations related to the diagnosis of HPV related disease by addressing cyto-virological correlations should also be an issue for the reference laboratory.
- To collaborate with other services specialised in surveillance of HPV-related diseases and evaluation of public health interventions such as cervical cancer screening and HPV vaccination.
- To represent Belgium in international networks of HPV reference laboratories.
- To contribute in education and training of virologists, laboratory technicians and pathologists in techniques of HPV testing.
- To set up expertise in serological testing for anti-HPV antibodies, which may be required to measure immunogenicity of HPV vaccines and for epidemiological studies.
- The reference laboratory should in the first place establish expertise (and infrastructure) in handling, storing and testing of samples which may contain HPV and collaborate with existing services with respect to epidemiological surveillance and programme evaluation. In addition, the reference laboratory must have expertise in management and handling samples from biobanks.
- The reference laboratory should preferentially not perform HPV tests in current clinical practice (as primary screening) or assure that the specific tasks related to the reference laboratory are independent from clinical testing activities.
- The reference laboratory should follow the state of the art and continuously update scientific and technical knowledge with respect to HPV testing and sample handling.

5.2 Quality control systems in cytological testing

In this section we mainly focus on the quality control of the negative cases.

5.2.1 How is it done abroad?

In 2007, European guidelines for quality assurance in cervical cancer screening were published, with specific recommendations for cytology laboratories[118]. The recommendations related to personnel and organization, material requirements, handling and analysis of cervical samples, recording of results are here not further described. The guideline describes also how the quality management should be set up to ensure optimal patients care and minimize the risk of liability claims. The internal quality management consists of a laboratory quality management (pre-analytical quality management), an analytical quality management and internal continuing education. The focus of this chapter is on the monitoring of the accuracy of screening, as described in the analytical quality management. Following three main methodologies for internal quality control of cytology are described in the guideline[118]:

- Rescreening of slides

  The procedures of rescreening may be designed to detect potential false negatives before final results are reported in order to improve patient care as well as individual and laboratory accuracy but also to monitor accuracy of screening, by measuring sensitivity and specificity or by monitoring detection rates of cytological abnormalities.

  Rapid review consists of re-screening quickly (30-120sec) all slides that are originally reported as within normal limits or as inadequate, in order to identify those that might contain missed abnormalities. These 'abnormal' slides are subsequently fully checked by an experienced cytotechnologist or cytopathologist.

  Rapid preview/prescreening of all smears is defined as partial microscopic inspection of a slide during a limited duration (max 120sec) before full routine examination. Advantages of this procedure are the rapid identification of most of the abnormal cases, the fact that the process is not influenced by previous markings on the slide and the fact that the gain in sensitivity is comparable to that of rapid reviewing and superior to that of 10% full rescreening.

Random rescreening of a random fraction of smears reported as negative is widely practiced in the Unites States (see section on practice in United States) but has been criticized for its lack of efficiency and statistical power.

Targeted rescreening of specific patients groups selects smears from patients with a higher risk of having cytological abnormalities (i.e. history of abnormal bleeding/spotting, history of recurrent cervical/vaginal infections, previous abnormal smears, and abnormal cervix appearance on colposcopy) and is done by a senior cytotechnologist of cytopathologist. This procedures has not yet been standardized and comparative data on the accuracy is lacking.

Automated rescreening could decrease the false-negative rates but is an expensive approach. However, the manual rescreening can be more expensive depending on the setting and volume.

- Monitoring screening detection and reporting rates

  Monitoring primary screening detection rates can be done by comparing the percentages of the main types of cytological findings (high-grade, low-grade, inadequate, undetermined, negative) detected by individual screeners to the laboratory as a whole or to local/national standards.

  Monitoring pathologists' reporting rates for low-grade, high-grade and inadequate results can be used as an outcome measure for primary screening performance.

- Correlation of cytology with clinical/histological outcome

  Cyto-clinical correlation consists of a comparison between all abnormal cytology reports with subsequent histopathology. The correlation process should be documented in the laboratory quality assurance programma and could serve as an internal education tool. The positive predictive value for high-grade cytology provides a measure of accuracy of cytology reporting.

  Cyto-virological correlation consists of the comparison between all abnormal cytology reports with HPV testing. The performance of a HPV test as triaging test is only accurate if HPV tests positive in at least of 30% of the patients with diagnosis of ASCUS.

  Audit of interval cancers contains the rescreening of negative or low-grade tests which resulted in a diagnosis of an invasive cancer less than 3-5years after the test. During rescreening, the assessor should also take into account the context of all components of the screening history, including cytological screening errors, sampling errors, non-compliance with follow-up recommendations, incomplete treatment and wheter or not the cancer was screen-detected. The rescreening should be done alongside negative and/or positive controls (with concealed labels) and should be performed by more than one cytopathologist/cytotechnologist.

Next to the internal quality management, also methodologies are proposed for the external quality management, such as:

- External continuing education

  This should be an important component of any quality assurance program and could contain different methods, such as workshops, symposia, proficiency testing, membership of societies for cytology etc. Inter-laboratory slide review sessions have shown to increase the reproducibility of cytology interpretation between participating laboratories.

- External quality control of screening skills

  External quality control can be done in different ways, such as proficiency testing (e.g. QUATE test), regular examination of test cases, monitoring of staining procedures, laboratory and personal reporting rates for high-grade and low-grade cytological abnormalities, and comparing results with national standards.

- Accreditation of the laboratory unit

  The external quality assessment of a laboratory should be done based on predefined standards. The external audits for laboratories are often done by international/national accreditation agencies (e.g. ISO).

As mentioned in the guideline itself, the above-mentioned quality standards are not yet implemented in all European countries. This guideline[118] is a first step in generating one common framework for the elaboration of a national quality program.

In the **United States**, a number of quality assurance measures were specified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) and were described in the cervical cytology practice guideline,

written by the American Society of Cytopathology[119]. In this guideline the different quality control activities are described such as:

- Pre-analytical quality control: relating to specimen receipt, preparation and staining, microscope and instrument maintenance and calibration;
- Screening and reporting of gynecologic specimen: the requirement of a qualified cytotechnologist or pathologist in a certified laboratory, with workload limits and maintaining work logs;
- Review of abnormal gynecologic cases: a reactive, reparative, atypical premalignant, or malignant specimen initially evaluated by a cytotechnologist must be referred to a pathologist for final interpretation and final report, also peer review is often included;
- Cytology-histology correlation and clinical follow-up: all premalignant and malignant gynecological cytology report must be compared with subsequent histopathology using the cytohistologic correlations. If no histological material is available, other follow-up material or information on the patient (via the ordering physician) must be attempted;
- Retrospective reviews: if a new high grade squamous intraepithelial lesion or carcinoma is detected, all negative cervical cytology from the last 5 years must be reviewed and significant discrepancies must be reported in an amended report;
- Measures of screening performance: evaluation of individual performance in comparison to overall laboratory performance. The most frequently used measures are described below (the evaluation of negative cases);
- Proficiency testing and continuing medical education: no national system for proficiency testing has been elaborated but some state and private programs are set up (e.g. State of Maryland Gynecologic Cytopathology Proficiency Program), the requirements for continuing medical education vary between states and professional societies.

Next to the above-mentioned quality control activities, the rescreening of the negative cases can be seen as a measure of screening performance. A false negative is defined as a negative cervical cytology test result in a woman with a cervical squamous or glandular inthraepithelial lesion or cancer. False negative results may be a consequence of patient sampling by the clinician or laboratory screening or interpretation. A laboratory screening or interpretative false negative is one in which abnormal cells are present on the slide, but are not identified by screening or misinterpreted after begin noticed during screening. The calculation of the false negative proportion (FNP) (i.e. false negative reports divided by the total number of women screened who have a cervical abnormality (true positives + false negatives)) requires a 100% rescreening of negative cases but for feasibility reasons the FNP is estimated based on rescreening a randomly selected sample of cases. This false negative proportion represents an estimate of the staff's average screening sensitivity.

In the CLIA '88 regulations[120] is specified that at least 10% of samples interpreted as negative by each cytotechnologist must be rescreened by a pathologist or a qualified supervisory cytotechnologist prior to reporting. Specimens from women at increased risk for cervical cancer must be included in the review process. The laboratory must have a clearly defined policy of its definition of increased risk as well as its method for random selection of the cases. Also a clear definition on the threshold to become a positive case is needed: a false negative threshold of either ASCUS or LSIL may be used, but the LSIL threshold is preferred.

To evaluate the individual performance in comparison to overall laboratory performance following measures are most frequently used: random rescreening, targeted rescreening of specific patient groups, seeding abnormal cases into the screening and rescreening pools and retrospective rescreening of negative cervical cytology specimens from patients with a current high grade abnormality. Nevertheless the different efforts made to optimize the individual and laboratory performance, this performance measure is subject to biasing effect of knowledge of outcome. Efforts to minimize this bias can be: review by multiple individuals, review without knowledge of clinical outcome and reviews of the index case embedded in a slide sequence containing a range of normal and abnormal cases. Another device to enhance the conventional cervical cytology testing is the use of automated screening devices. These devices rely on computer analysis of digitized images of cells to triage cervical cytology slides for subsequent identification of premalignant and malignant changes. Potential benefits of these automated screening devices include the reduction of false negatives rates, the increase of sensitivity and the increase of throughput for the laboratory.

The British Society for Clinical Cytology published in 2010 an updated version of the 'Recommended code of practice for laboratories participating in the UK cervical screening programmes'[121]. The BSCC recommend that rapid screening is the method of choice for routine quality control of primary screening. Rapid screenig is the most cost effective way of preventing false negative reports and allow monitoring of the accuracy of screening within the laboratory and between individual staff members. Looking at all samples, including the negative and inadequate samples, facilitate the identification of patterns of poor performance. Following recommendations are made by the BSCC:

- Rapid screening must only be carried out by qualified members of staff
- There is no evidence as to the ideal technique for rescreening and no single technique is recommended. However the rescreen should take approximately one minute to 90 seconds and aim to cover a representative area of the cellular material. No individual should rapid screen more than 50 tests in a 24 hour period
- Individuals should undergo basic training in the different skills and techniques involved in rapid screening before they are permitted to carry it out
- Some form of in house assessment or evaluation should be undertaken after the first month
- Rapid screening itself should be subject to quality management.

No choice is made between rapid re-screening and pr-screening. The expectation of normality inherent to rapid rescreeing, because most of the abnormal slide have alreadyb been identified and removed, could be avoided by rapid pre-screening. If rapid pre-screening is used, still all original slides (normal and abnormal) should be included in the primary screening workload. An advantage of rapid pre-screening is the enhanced continual assessment of an individual's screening performance. In both methodologies, the results must be completed blinded to each other and carried out by different individuals.

In addition to assessment of performance, the BSCC recommends that all individuals participate in relevant continuing education schemes and activities. Also each individual reporting cervical cytology samples in the UK cervical screneing programmes must participate in a recognised external quality assurance (EQA) scheme.

The National Cancer Screening Service (**Ireland**) has set up guidelines for quality assurance in cervical screening (2009)[122]. Within this guideline a chapter is dedicated on the quality assurance in cytopathology. Three main methodologies for internal quality control are suggested: methods based on re-screening of slides, methods based on monitoring screening detection and reporting rates, and methods based on correlation of cytology with clinical/histological outcome. Only the methods based on re-screening are in scope of this report.

The following re-screening procedures are proposed to increase the sensitivity of cytological screening:

- Rapid review of smear tests initially reported as negative or inadequate: manually quickly (120seconds) rescreening of normal slides, followed by a full check of the suspect smear tests by an experienced cytotechnologists or cytopathologist;
- Rapid preview/pre-screening of all smear tests: partial microscopic inspection of a slide during limited time (120seconds) before full routine examination;
- Targeted re-screening of specific patient groups: rescreening of smear tests from patients known to be at higher risk of having cytological abnormalities (history of abnormal bleeding/spotting, history of recurrent cervical/vaginal infections, previous abnormal smear tests, an abnormal cervix appearance on colposcopy), done by senior cytotechnologist or cytopathologist;
- Automated re-screening: an automated screening platform scans each slide and identifies 22 fields out of a 120 that contain cells of interest, the cytotechnologist reviews these 22 fields using an automated microscope

Next to the different methods to improve the quality control in the laboratory, key performance indicators for cytopathology are formulated on following topics:

- Laboratory turnaround time;
- Laboratory sensitivity and specificity for all scientific staff, including sensitivity data per risk grade result profile;

- Cythopathologist workload;
- Histopathology/cythopathology correlation.

In **the Netherlands**, the screening program is in full transformation from a cytological screening to a HPV screening in first line[123]. Cytological analysis will only be performed after a positive HPV test. If the cytological test (primary cytology) is negative, a follow-up PAP smear test with cytological analysis (secondary cytology) will be performed after 6 months.

The Dutch Association for Pathology developed a practice guideline on the quality guarantee for the cytopathological analysis in laboratories[124]. Following selection of quality indicators on the follow-up and surveillance are described:

- Carcinoma audit: all cervix carcinoma need to be linked to previous cytological analyses (up to 6 years)
- Follow-up: collection of all referral advices
- Feedback towards clinicians on the percentage of specimens with insufficient quality for further analysis

Similar to the other countries and the European guidelines, an internal audit and external quality assessment are described in the guideline. No details are provided on the rescreening procedures of cytological tests.

5.2.2 Belgian situation

5.2.2.1 Belgian regulation

At present, the licensing of the Belgian laboratories for pathological anatomy consists of two different systems: the compulsory licensing by the FPS Health, Food Chain Safety and Environment and the optional accreditation by the FPS Economy.

The compulsory licensing is regulated by a royal decree of 5/12/2011 (valid from March 2013 onwards) which stipulates the content and set-up of a quality system. Each laboratory should have its own internal quality system, based on written standard procedures (Quality Manual) on all phases of the analyses, the circumstances of these analyses, the general organization of the laboratory and on the qualification of the personnel. In each laboratory a responsible is indicated for the set up and evaluation of the quality system. The requirements for this quality system are elaborated in a practice guideline[125], developed by the Commission for pathological anatomy and published in January 2014. In this guideline also some examples of quality indicators are presented, e.g. turnaround time, histopathology/cytopathology correlation, correlation HPV with ASCUS. Next to an internal quality control, each laboratory should also participate in the national external quality evaluation program, set up by the Commission for pathological anatomy. The external evaluation and the related statistical processing is done by the service Quality of medical laboratories within the WIV/ISP. This service is also member of the European Committee for External Quality Assurance Programmes in Laboratory Medicine (EQALM). The Commission of Pathology defines the technical fields that have to be evaluated and the frequency of these evaluations by WIV/ISP. This Commission also advises the Minister of Public Health about the licensing of labs and of all issues related to anatomic pathology in general, it also advises the National Council for Quality Promotion and the Technical Medical Council (RIZIV/INAMI) for issues related to the nomenclature. Different working groups (practice guidelines, external evaluation programmes, legislation) have been established since the installation of the Commission in October 2012[126].

The linkage between the compulsory recognition and the reimbursement system by the NIHDI (Art. 11 and art. 32 in the Belgian Nomenclature), made that all Belgian laboratories nowadays are recognized. Until now, the WIV/ISP is performing the external evaluation on the written standard procedures of each laboratory. The visitations on location are not yet done. Both the RD and the practice guideline are quite vague on the requirements for external quality evaluation, therefore specific recommendations are lacking on how the rescreening of negative cases should be performed.

The optional accreditation by the FPS Economy consists of the ISO 15189-standard for medical laboratories, which is assigned by BELAC (the Belgian accreditation organization of ISO). The ISO-standard specifies the quality management system requirements for medical laboratories, but no specific requirements are formulated for the PAP-tests. The evaluation of the quality system within the laboratory is done by audits. The majority of Belgian laboratories have obtained the ISO-accreditation.

The following Table 23 gives an overview of the main differences between the license and the accreditation.

Table 23 – Main differences between license and accreditation

Characteristics	Licensing of the laboratory	Accreditation of the laboratory
Legislative basis	RD 5/12/2011	RD 7/6/2007, RD 4/5/2009
Reimbursement of procedures (nomenclature)	Art 32, Art 33bis and Art 11	Art 33bis, Art 32 (HPV)
Scope of the evaluation	Conformity	Competence to perform specific tests
Criteria	RD 5/12/2011 and Practice Guideline	ISO 15189
Extent	The whole laboratory	Specific tests
Responsibility	FPS Public Health/Minister	FPS Economy
Evaluator	ISP/WIV / visits	BELAC / audits
Mandatory	Mandatory from 1/3/2013	Mandatory for labs molecular biology (oncology and virology) and for pathology labs performing molecular diagnostic tests

Source. Romaric Croes & Herwig van Dijck. L'AR du 5/12/2011 - Au sujet de la Commission d'Anatomie Pathologique et les implications pour nos laboratoires, 17.11.2012

A search on the websites of the Belgian laboratories for pathological anatomy revealed also other kinds of accreditation, such as the accreditation by the College of American Pathologists (CAP) and the accreditation by the Clinical Laboratory Improvement Amendments (CLIA). Both accreditation systems are described in the section on the international comparison.

5.2.2.2 Rescreening in Belgium

In an overview of the Belgian situation(Drijkoningen 2005[127], Arbyn 2000[2]) some figures are presented on the use of quality assurance methods: 65% of the cytology laboratories apply targeted rescreening (of women at risk), 17% rapid rescreening, 9% full double screening and 9% rescreening of 10% of the slides. Next to rescreening of slides, also the cyto-histological correlation is systematically performed (in 94% of all laboratories) and continuous education for the cytotechnicians is offered (in 88% of all laboratories).

After phone consultation with a selected number of laboratories (list in appendix), the following rescreening mechanisms were mentioned:

- Rescreening by cytotechnologist and pathologist of a random sample of 10 smear tests per 3500 smear tests
- 10% rescreening of negative smear tests and in addition an external quality control by external company (Hologic)
- 10% rescreening of random sample (positives and negatives) and in addition external quality control by external company (1x/year)
- In case of new HSIL diagnosis, all previous cytological analyses (up to 5 years) are reviewed + correlation between cytology and biopsy

During an expert meeting (see more explanation in the discussion), the experts mentioned the rescreening program in the Bordet Institute. If a CIN3 is diagnosed, all previous cytological tests are re-analysed.

The above-mentioned list indicates a great variety between laboratories. This variety is probably due to lack of formal regulation. Each of the laboratories have developed their own strategy of quality control, taking into account financial and organisational aspects of this additional procedure within their quality management system.

5.2.3 Effectiveness of rescreening methods

This sections gives only an overview of the existing systematic reviews on the effectiveness of different rescreening methods. A more systematic and broaden approach is needed to determine the potential advantages and disadvantages of each method.

Rapid prescreening

Rapid prescreening is the partial microscopic inspection of a slide during a limited duration (maximum 120 seconds) before a full routine evaluation. The difference with rapid reviewing is that in rapid prescreening all slides are quickly scanned by the cytotechnologist while in rapid reviewing only the slides initially interpreted as negative are reviewed[128].

One meta-analyses was found on the accuracy of rapid prescreening compared to full screening of Pap smears[128]. The pooled analysis of 6 studies showed an average sensitivity of rapid prescreening relative to the combination of subsequent full screening of 64.9% (95% CI: 50.7-79.1%) for all abnormalities (ASCUS or more severe), 72.6% (95% CI: 60.0-85.2%) for LSIL or more severe and 85.7% (95% CI: 77.8-93.6%) for HSIL or more severe. The pooled specificity was 96.8% (95% CI: 95.8-97.8%). The prevalence of cytologic abnormalities ranging from 2.7% to 4.7%, resulted in a pooled PPV of 60.4% (95% CI: 49.6-71.2%). The pooled NPV was 97.4% (95% CI: 96.2-98.5%). The overall proportion of additional positive slides was 2.8% (95% CI: 0.0-5.8%). A subanalysis, taking into account the duration of the rapid prescreening process, showed an overall increase of the sensitivity by increasing reading time and severity of cytologic abnormality. A multivariate analysis using the sensitivity as a dependent variable and duration of prescreening, the number of slides per session, the

mode of slide movement and the cytologic threshold as predictor variables showed following results:

- Increase in sensitivity of 7.0% (95% CI: 4.8-18.9%) for LSIL or more severe compared to the baseline threshold (ASCUS or more severe), but not significant (p=0.24);
- Increase in sensitivity of 23.2% (95% CI: 11.1-35.2%) for HSIL or more severe compared to the baseline threshold (ASCUS or more severe), highly significant (p=0.000);
- Increase in sensitivity of 0.26% (95% CI: 0.09-0.42%) for every second above 30 seconds (duration);
- Decrease in sensitivity of 0.68% (no CI mentioned) per slide per session (workload);
- No change in sensitivity with change in mode of slide movement.

One study of the meta-analysis[128] looked at the sensitivity of rapid prescreening in relation to experience of the cytotechnologists: the sensitivity was substantially higher for ASCUS or more severe (p=0.02) for the more experienced cytologists but the difference between inexperienced an experienced cytologists is smaller for LSIL or more severe (p=0.07) and even no significant difference for HSIL or more severe.

The results show how the (increased) duration of screening, the (increased) experience of the cytologists and the (decreased) workload in the laboratory can influence (positively) the performance of the screening procedure. The authors conclude that rapid prescreening shows considerable promise as a quality control process with a sensitivity gain comparable to rapid reviewing and is superior to that of 10% full rescreening.

Rapid reviewing

Rapid or partial reviewing is defined as partial rescanning of slides, previously reported as within normal limits or as inadequate, for a limited duration, which varies throughout the literature between 30 and 120 seconds[129]. This method has the advantage that false negatives which were missed at initial screened are detected on quick manual rescreening. Rapid reviewing differs from the approach in the United States, in which full rescreening is performed of a 10% random sample of the negative workload. The meta-analysis of Arbyn 2000[129] shows that on average 1.8% of abnormal smears, 0.9% SIL and 1.4% HSIL could be detected with rapid reviewing. The more appropriate pooled random-effect estimation shows 2.7% (95% CI: 1.8-3.5) for lesions ≥ASCUS, 1.3% (95% CI: 0.7-2.0) for SIL and 1.4% (95% CI 0.8-2.1) for HSIL. The pooled estimation of the percentage of positive slides is 0.18% (95% CI: 0.14-0.21) for all cytological abnormalities, 0.07% (95% CI: 0.05-0.09) for lesions of at least LSIL and 0.02% (95% CI: 0.01-0.03) for HSIL or worse. The specificity was estimated as 97.2% (95% CI: 96.4-98.1) and the positive predictive value of the suspicion of abnormality was 8.6% (95% CI: 5.3-11.9%). If full rescreening is performed on the whole data set, the detection of abnormalities is 2.1 times more than rapid reviewing. However, in daily practice, only on a 10% random sample this full rescreening is performed. Comparing the results of 10% rescreening and rapid reviewing, shows an increased detection rate with rapid reviewing: 4.7 times more extra positives, 5.6 times more SIL, 7.9 times more high grade lesions. The authors conclude that rapid reviewing is superior to 10% random rescreening.

Cyto-virological correlation

The meta-analysis of Arbyn 2009[130] focuses on the use of an HPV tests as quality control method in cytopathology. On average 43% (95% CI: 40-46%) of women with ASCUS/ASC-US and 76% (95% CI: 71-81%) of women with LSIL were high-risk HPV positive. A consistent and statistically significant negative trend in hrHPV with increasing age was observed in both groups. High-risk HPV positivity rates could be used to identify laboratories or cytotechnologists that overcall or undercall equivocal or low-grade abnormalities. The authors consider 25-61% as benchmark for equivocal squamous cytology and 57-95% for low-grade lesions.

5.2.4 Discussion

This chapter is presented to a working group of Belgian experts involved in the Belgian quality procedures (name and affiliation can be found in the colophon).

During this meeting the results were discussed and they provided more details on the current practice. Following comments were quoted:

- The quality control of HPV and cytological tests should be a phased approach, starting with a validated internal quality control towards a external quality control with comparison with other laboratories.
- The lack of clear nomenclature codes hampers the transparency of the current practice.
- Quality control is an important topic, but two other issues were also mentioned as important for further research:
  - The higher coverage in the French-speaking region, nevertheless the absence of a organised screening program. This could imply that the current system of invitations send by mail (in the current screening program in the Flemish region) does not obtain the expected results. The experts emphasised the need for more primary research on the impact of the letter invitations.
  - Often the gynecologist chooses to use the device for liquid-based cytology but without informing the patient on the additional costs related to this kind of cervical smear test. If this gynecologist is conventioned, additional costs can not be charged to the patient and are thus paid by the laboratory itself. If the gynecologist is not conventioned, additional costs for liquid-based cytology are charged to the patient. The difference in costs between conventional and liquid-based cytology could be solved by an equal reimbursement of both techniques by the NIHDI. The difference in costs due to the convention status of the clinician is out-of-scope for this report.
- The effort of reviewing is considerable (time-consuming) and the level of evidence on reviewing methods is quite low which contrasts with the evidence of double reading of mammograms. Preferred methodologies for quality control were: the use of rates of CIN3 and ASC-US and the use of histological correlation. All experts agreed that further consensus between pathologists is needed and that a recommendation would be formulated on the role of the commission for Pathological Anatomy in elaborating this consensus agreement. Also the initiative at the Bordet Institute (rescreening of all previous cytological tests if a cancer is diagnosed) is well approved and could be an example for rescreening with educational aims (without the aim to punish poor performance of individuals or laboratories).
- Some concerns were made on the impact of prolongating the time interval between screening (from every 3 years to every 5 years) on the increased doubtful samples to ensure the correct diagnosis.
- The experts mentioned also the lack of quality assurance procedures for colposopy. This issue is out of scope for this project, but can be incorporated in the recommendation on topics for further research.

5.2.5 Conclusion

In Belgium, the setup of a quality assurance procedure are still in a primary phase, with no consensus on which quality methods are needed for cytological analyses, and especially the rescreening of negative cases.

The lack of clear quantitative data on the used quality procedures, hampers the description of the current practice in Belgium. The restricted description of the Belgian situation, based on reports and phone interviews, indicate a variety in quality procedures between the laboratories. A consensus between the pathologists on the appropriate methods will increase the overall performance of the laboratories. For HPV testing, the elaboration of a national reference laboratory will be in line with the international developments.

6 CHARACTERISTICS OF CYTOLOGICAL SCREENING, CURRENT PREVALENCE OF HPV INFECTION, (BY AGE, CYTOLOGY, AREA), CYTO-VIROLOGICAL CORRELATION

6.1 Introduction

The answer to the question whether HPV-based screening should be introduced in Belgium, should in the first place be based on the assessment of its efficacy and effectiveness (covered in 1.2) and its cost-effectiveness (assessed in 8). However, to estimate the burden of switching from cytology to HPV virology as the primary screening test on the public health system, more epidemiological key parameters are needed, such as proportion of women having a positive screen test result (cytology, HPV and correlation) by age group and geographical localisation.

In this chapter, we will estimate the prevalence of cervical cytology findings (NILM, ASC-US, AGC, L-SIL and H-SIL), the prevalence of HPV infection (grouped as high-risk infection and by separate hrHPV genotype) as well as the correlation between both.

To address these questions, cytology and HPV test results from a large Belgian cytopathology lab performing HPV testing on all cervical cell specimen since 2006 will be used.

6.2 Material and methods

6.2.1 Study population and used tests

In agreement with the aims of the current HTA review, a request has been sent to the AML laboratory in Antwerp to provide an anonymised dataset containing individual data including the following variables:

- a numerical anonymous ID code which is constant at the individual level allowing for longitudinal analysis
- the post code of the residence
- the year of birth
- reason for the collection of a cervical cell specimen (screening or follow-up because of a previous cervical abnormality, or surveillance after treatment of cervical precancer). For a group of smears that were not reimbursed by INAMI/RIZIV, the distinction was not made.
- speciality code of the smear taker
- date of Pap smear collection
- result of the cytological interpretation categorised according to the Bethesda system[65]
- quality of the specimen with respect to amplifyability of DNA
- presence of DNA of high-risk HPV genotypes.

The purpose of this section was to update a previous report which was restricted to Pap smears taken in October 2006[73]. The request was sent on the 21st of November 2013. An agreement on conditions of data transfer was reached on the 8th December 2013 and a data set was provided to the Scientific Institute of Public Health on the 23rd of December 2013.

A more comprehensive data set will be generated early 2014 containing data on histology, treatment and vaccination status.

All samples were liquid-based using the Surepath technology (Tripath, Burlington, North-Carolina, USA). All slides are prescreened using the FocalPoint®, a computerized scanning system for the primary screening of cervical smears (Tripath, Burlington, North-Carolina, USA). Presence of HPV genotypes was determined on all samples using a multiplex *Taq*Man-based real-time quantitative PCR targeting type specific sequences of viral E6 or E7 genes: HPV6 E6, HPV16 E7, HPV18 E7, HPV31 E6, HPV33 E6, HPV35 E4, HPV39 E7, HPV45 E7, HPV51 E6, HPV52 E7, HPV53 E6, HPV56 E7, HPV58 E6, HPV59 E7, HPV66 E6 and HPV68 E7[131]. The following HPV types were considered as being high-risk: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68[132, 133]. Slides were interpreted with pre-knowledge of the virological result[134].

Real time quantitative PCR for β-globin was used to verify the quality of DNA in the sample and to measure the amount of input DNA. However, no data on viral load were provided.

The used PCR test fulfills the clinical performance criteria for use in primary screening for cervical cancer[44, 135].

In principle, cytologically positive women (ASC-US or worse) were followed according current guidelines defined by VVOG and BSCC[136] which are in agreement with European recommendations[50, 137]. Cytologically negative but HPV positive women were retested 12 months later.

6.2.2 Study questions

The following objectives were addressed:

- To assess the prevalence of high-risk HPV infection of individual HPV-genotypes in the study population and stratified by cytological findings and by age.
- To assess the cross-sectional association between HPV infection (hrHPV infection and infection with individual hrHPV types) and cytological abnormalities.

6.2.3 Statistical analysis

The statistical package STATA, version 10.1 (Stata Corp., College Station, Texas, US) was used for data analysis. A large series of standard tables with monovariate and bivariate distributions were made. Statistical inference was not assessed systematically, since the enormous size of study population would makes small differences between groups and categories nearly always statistically significant.

Crude and age-standardised prevalences were computed using the European Standard Population as reference using methods for binomial distributions[138].

Crude and age-standardised prevalences were computed using the European Standard Population as refereence[12] using methods for binomial distributions[13].

We computed the relative (RR) and attributed risks (AR) for cytological abnormalities associated with HPV infection and individual HPV geno-types. The risk attributed to exposure (AR_{exp}) to a risk factor is defined as the difference in risk between the exposed and the non exposed subjects over the risk among the exposed, or in formular terms:

$$AR_{\exp} = \frac{R_{\exp} - R_{n.\exp}}{R_{\exp}},$$

where R means risk for a cytological lesion, and the index (exp) stands for infected with a genotype and (n.exp) stands for not-infected by that genotype. The attributable risk among the exposed can also be expressed as:

$$AR_{\exp} = \frac{RR-1}{RR}$$

The AR_{exp} is often used in vaccinology to express vaccine efficacy: it represents the reduction in vaccine-type associated lesions if infection with that type is eliminated by a 100% effective prophylactic vaccine assuming absence of cross-protection.

Another important concept in preventive medicine is the population attributable risk (AR_{pop}).

$$AR_{pop} = \frac{R_{pop} - R_{n.\exp}}{R_{pop}}$$

AR_{pop} can also be expressed as:

$$AR_{pop} = \frac{p(RR-1)}{p(RR-1)+1}$$

AR_{pop} = equivalent to the reduction in the burden of a lesion in the whole population if a 100% effective vaccine prevents all infections with a particular type (assuming no cross-protection and no type replacement). The population attributable risk depends on the relative risk for a certain disease (for instance HSIL) associated with the risk factor (for instance infection with a HPV16) and the prevalence of the risk factor (prevalence of HPV16 in the population).

The change in risk of cytological abnormalities by increasing number of high-risk HPV infections was assessed by a chi2 trend which generalizes the Wilcoxon test to several ordered groups[139].

The multivariate relation between presence of HSIL, different HPV-genotypes and other factors was assessed by logistic regression[140].

6.3 Results

6.3.1 Study and population characteristics

6.3.1.1 Age composition and period of collection

The received data file contained 707 233 records from cervical cell specimens collected between the 1st of October 2006 and the 31st of October of 2013 (see Table 24).

Table 24 – Period of collection of the cervical cell specimen

Year of collection	Number	%
2006	25 743	3.6
2007	101 226	14.3
2008	106 916	15.1
2009	97 193	13.7
2010	90 621	12.8
2011	108 528	15.4
2012	104 059	14.7
2013	72 947	10.3
Total	707 233	100.0

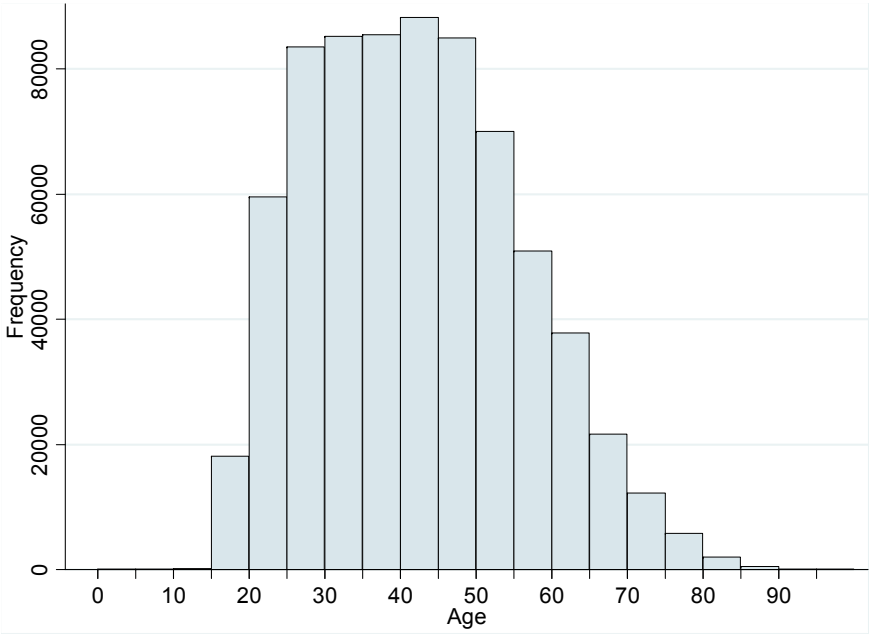
The age varied between 0 and 99 years, with a median of 41 and an interquartile range of 30-41 (see Table 25 and Figure 38).

Table 25 – Age composition of the study population

Age group (years)	Number	%
0-4	9	0.0%
5-9	9	0.0%
10-14	195	0.0%
15-19	18 116	2.6%
20-24	59 508	8.4%
25-29	83 519	11.8%
30-34	85 186	12.1%
35-39	85 463	12.1%
40-44	88 191	12.5%
45-49	84 939	12.0%
50-54	69 991	9.9%
55-59	50 912	7.2%
60-64	37 838	5.4%
65-69	21 638	3.1%
70-74	12 278	1.7%
75-79	5 769	0.8%
80-84	2 016	0.3%
85-89	519	0.1%
90-94	72	0.0%
95+	11	0.0%
Total	706 179	100.0%

Note: 1054 women with improbable or unknown birth year are excluded.

Figure 38 – Age composition of the study population



Eighty three percent of samples were taken from women in the target age group (25-64 years), whereas eleven percent were younger and six percent were older (see Table 26).

Table 26 – Proportion belonging or not belonging to the target age group for cervical cancer screening

Age group (years)	Number	Percent
<25	77837	11.0%
25-64	586 039	83.0%
≥65	42 303	6.0%
Total	706 179	100.0%

6.3.1.2 Geographical origin

The origin of women by province is shown in Table 27. Most of the samples (85%) were from three provinces (Antwerp, East- and West-Flanders).

6.3.1.3 Cumulative number of cervical cell specimen by woman

All the 707 233 specimen were collected from 319 852 women. 149 231 women contributed only one specimen to the study, whereas 170 629 women contributed two or more specimen. Women with two or more Pap smears had on average 3.3 Pap smears (range 2-19) (Table 28).

6.3.1.4 Reason for collection of the cervical cell specimen

Since 29 June 2009, a new administrative code was introduced for collection and interpretation of Pap smears allowing the distinction of the clinical indication. Seventy two percent of the Pap smears were collected for reason of screening, 19% was taken because of follow-up of a previous abnormality or surveillance after treatment of cervical cancer and 9% concerned rescreening. This rescreening is in principle a second interpretation of a smear interpreted as ASC-US (Table 29).

Table 27 – Origin of the samples, by province (4778 samples were from women with unknown origin or were associated with a non-existing or non-Belgian postal code)

Province	Number	%
Antwerpen	346 066	49.3%
W-Vlaaanderen	124 703	17.8%
O-Vlaanderen	128 486	18.3%
Hainaut	4545	0.6%
Liège	559	0.1%
Limburg	27 387	3.9%
Luxembourg	243	0.0%
Namur	535	0.1%
Vlaams-Brabant	40 143	5.7%
Brussels	27 037	3.8%
Brabant-Wallon	2751	0.4%
Total	702 455	100.0

Table 28 – Total number of Pap smears taken over the study period from individual women

Cumulative number of specimen	Nb of women	% of women	Nb of smears	% of Pap smears
1	149 231	46.66%	149 231	21.10%
2	68 783	21.50%	137 566	19.45%
3	43 614	13.64%	130 842	18.50%
4	28 868	9.03%	115 472	16.33%
5	14 435	4.51%	72 175	10.21%
6	8 166	2.55%	48 996	6.93%
7	3 891	1.22%	27 237	3.85%
8	1 438	0.45%	11 504	1.63%
9	704	0.22%	6 336	0.90%
>=10	722	0.23%	7 874	1.11%
Total	319 852	100.00%	707 233	100.00%

Table 29 – Reasons for collection and interpretation of the Pap smears

Reason	Number	%
Missing	413	0.1%
Screening	298 947	71.9%
Follow-up	76 837	18.5%
Not reimbursed	39 704	9.5%
Total	415 901	100.0%

6.3.2 Cytological findings

In Table 30, the absolute numbers and the prevalence of cervical cytology findings are presented for the two periods (before and after 28 June 2009). A substantial decrease in normal interpretations (NILM) is observed (from 91% to 87%), which is essentially due to an increase in LSIL (from 3.6% to 6.1%).

Table 30 – Frequency of cytological results (absolute number & prevalence [in%], by period)

Category	N and % of total	< 29 June 2009	≥ 29 June 2009	Total
Unsatisfactory	N	370	501	871
	%	0.13	0.12	0.12
NILM	N	264 410	363 259	627 669
	%	90.76	87.34	88.75
ASC-US	N	11 546	20 082	31 628
	%	3.96	4.83	4.47
AGC	N	656	912	1 568
	%	0.23	0.22	0.22
LSIL	N	10 387	25 304	35 691
	%	3.57	6.08	5.05
ASC-H	N	1 118	1 955	3 073
	%	0.38	0.47	0.43
HSIL	N	2 845	3 882	6 727
	%	0.98	0.93	0.95
AIS	N	0	1	1
	%	0	0	0
Sq Ca	N	0	1	1
	%	0	0	0
AdenoCa	N	0	4	4
	%	0	0	0
Total	N	291 332	415 901	707 233
	%	100	100	100

Since 29 June, separate statistics by clinical indication for taking or interpreting the Pap smear can be produced (see Table 31). The prevalences of cytological abnormalities are substantially higher in the *follow-up* group compared to the *screening* group: 3.5 times more ASC-US, 2.2 times more AGC, 4.9 times more LSIL, 4.8 times more ASC-H and 5.6 times more HSIL+ (see Table 31). The missing group showed similar prevalence profiles as the follow-up group, whereas the not-reimbursed groups showed a prevalence of cytological abnormalities which was lower than in the screening group (Table 32).

Table 31 – Frequency of cytological results (absolute number & prevalence [in%]), by clinical reason for Pap smear collection or interpretation, for the period 29 June 2009 – 31 October 2013

Category	N and % of total	Missing	Screening	Follow-up	Not reimbursed	Total
Unsatisfactory	N	4	311	76	110	501
	%	0.96	0.10	0.10	0.28	0.12
NILM	N	279	275 161	50 822	36 997	363 259
	%	67.23	92.04	66.14	93.18	87.34
ASC-US	N	41	9 923	8 969	1 149	20 082
	%	9.88	3.32	11.67	2.89	4.83
AGC	N	5	547	310	50	912
	%	1.20	0.18	0.40	0.13	0.22
LSIL	N	67	10 618	13 393	1 226	25 304
	%	16.14	3.55	17.43	3.09	6.08
ASC-H	N	8	840	1 042	65	1 955
	%	1.93	0.28	1.36	0.16	0.47
HSIL	N	9	1 544	2 222	107	3 882
	%	2.17	0.52	2.89	0.27	0.93
AIS	N	0	0	1	0	1
	%	0.00	0.00	0.00	0.00	0.00
Sq Ca	N	0	1	0	0	1
	%	0.00	0.00	0.00	0.00	0.00
AdenoCa	N	0	2	2	0	4
	%	0.00	0.00	0.00	0.00	0.00
Total	N	415	298 947	76 837	39 704	415 901
	%	100.00	100.00	100.00	100.00	100.00

Table 32 – Prevalence ratios in the groups follow-up, missing and not reimbursed compared to the screening group

	Relative prevalence (compared to screening group)		
Category	Follow-up	Missing	Not reimbursed
Unsatisfactory	0.95	9.27	2.66
NILM	0.72	0.73	1.01
ASC-US	3.52	2.98	0.87
AGC	2.20	6.58	0.69
LSIL	4.91	4.55	0.87
ASC-H	4.83	6.86	0.58
HSIL+	5.60	4.19	0.52

6.3.3 Virological findings (monovariate analysis)

Fourteen percent of tested women had a hrHPV infection in the period before 28 June and 18% after that date (see Table 33). In the second period the prevalence of hrHPV was 12% and 46% (see Table 34). The prevalence in women who were not reimbursed was 10% whereas that in the group where the indication was missing was 45%. The prevalence of separated by individual HPV genotype is shown only for women age 25-64 of the screening group in the second period (Table 35).

Table 33 – Prevalence of hrHPV infection in the study population, in period 1 (<28 June 2009) and period 2 (>28 June 2008)

hrHPV	Period 1	Period 2	Total
N	291 030	415 442	706 472
n+ (13 types)	40 383	74 890	115 273
%+	13.9%	18.0%	16.3%

Table 34 – Prevalence of hrHPV infection in period 2, by indication of Pap smear collection

hrHPV	Missing	Screening	Follow-up	Not reimbursed	Total
N	410	298 642	76 785	39 607	415 444
n+ (13 types)	186	35 380	35 225	4100	74 891
%+	45.4%	11.8%	45.9%	10.4%	18.0%

Table 35 – Prevalence of individual HPV types (ranked from high to low), hrHPV infection, infection with HPV16 or 18 and other hrHPV types among women aged 25-64 year attending screening after 28 June 2009

HPV type	rank	n+	%+
HPV16	1	7 243	2.95%
HPV31	2	5 523	2.25%
HPV53	3	4 362	1.78%
HPV51	4	3 425	1.39%
HPV39	5	3 272	1.33%
HPV52	6	3 272	1.33%
HPV56	7	2 857	1.16%
HPV66	8	2 667	1.09%
HPV59	9	2 434	0.99%
HPV18	10	2 242	0.91%
HPV58	11	1 961	0.80%
HPV33	12	1 319	0.54%
HPV06	13	1 251	0.51%

HPV35	14	1 177	0.48%
HPV45	15	820	0.33%
HPV68	16	650	0.26%
HPV11	17	325	0.13%
hrHPV (13 types)		26 750	10.89%
HPV1618		9 150	3.72%
other hrHPV		17 600	7.16%
Total		245 715	

HPV16 is the most prevalent type (2.95%), followed by HPV31 (2.25%) and HPV53 (1.78%) (see Table 35). HPV18 ranked only at the 10th place with 0.91%. About eleven percent carried a hrHPV infection. HPV16 or 18, the two oncogenic types HPV targeted by the current prophylactic vaccines are found in 3.72%. The low-risk types HPV6 and HPV11 are found in respectively 0.51% and 0.13%.

6.3.4 *Prevalence of HPV infection stratified by cytological category*

The distribution of HPV types in each cytological category is shown in Table 36 for women in the screening group collected after 28 June 2009 with a satisfactory Pap smear and amplifiable DNA. The prevalence of hrHPV infection increased from 6% in NILM to 93% in HSIL. HPV16 was the most prevalent genotype in NILM (1.5%), followed by HPV31 (1.3%) and HPV53 (1.0%). In HSIL, also HPV16 was the most prevalent type (48%), followed by HPV31 (16.3%), HPV52 (15%), HPV51 (12%) and HPV18 (10%). In HSIL, 55% carried HPV16 or HPV18, and 38% carried other hrHPV types.

Table 36 – Prevalence of HPV types by cytological category (absolute number and prevalence) (Restricted to the period > 28 June 2009 and screening group)

		NILM	ASC-US	AGC	LSIL	ASC-H	HSIL+	TOTAL
Total	N	227 623	7 751	463	7 617	703	1 325	245 482
hr13	n+	14 416	4 720	107	5 677	590	1 235	26 745
	% (n+/N)	6.3	60.9	23.1	74.5	83.9	93.2	10.9
h06	n+	557	246	7	388	17	36	1 251
	% (n+/N)	0.2	3.2	1.5	5.1	2.4	2.7	0.5
h11	n+	161	56	2	93	7	6	325
	% (n+/N)	0.1	0.7	0.4	1.2	1.0	0.5	0.1
h16	n+	3 353	1 285	35	1 662	263	644	7 242
	% (n+/N)	1.5	16.6	7.6	21.8	37.4	48.6	3.0
h18	n+	1 132	397	24	503	60	126	2 242
	% (n+/N)	0.5	5.1	5.2	6.6	8.5	9.5	0.9
h31	n+	2 969	979	23	1 194	141	216	5 522
	% (n+/N)	1.3	12.6	5.0	15.7	20.1	16.3	2.2
h33	n+	538	262	5	358	36	120	1 319

	% (n+/N)	0.2	3.4	1.1	4.7	5.1	9.1	0.5
h35	n+	622	193	2	275	24	61	1 177
	% (n+/N)	0.3	2.5	0.4	3.6	3.4	4.6	0.5
h39	n+	1 655	526	7	916	47	121	3 272
	% (n+/N)	0.7	6.8	1.5	12.0	6.7	9.1	1.3
h45	n+	413	134	4	219	13	37	820
	% (n+/N)	0.2	1.7	0.9	2.9	1.8	2.8	0.3
h51	n+	1 499	613	7	1 090	57	158	3 424
	% (n+/N)	0.7	7.9	1.5	14.3	8.1	11.9	1.4
h52	n+	1 379	740	11	858	84	198	3 270
	% (n+/N)	0.6	9.5	2.4	11.3	11.9	14.9	1.3
h53	n+	2 265	683	12	1 226	61	115	4 362
	% (n+/N)	1.0	8.8	2.6	16.1	8.7	8.7	1.8
h56	n+	1 372	474	2	875	40	94	2 857
	% (n+/N)	0.6	6.1	0.4	11.5	5.7	7.1	1.2
h58	n+	821	413	7	552	47	121	1 961
	% (n+/N)	0.4	5.3	1.5	7.2	6.7	9.1	0.8
h59	n+	1 300	407	8	602	41	75	2 433
	% (n+/N)	0.6	5.3	1.7	7.9	5.8	5.7	1.0
h66	n+	1 321	369	9	860	31	77	2 667
	% (n+/N)	0.6	4.8	1.9	11.3	4.4	5.8	1.1
h68	n+	264	127	3	225	7	24	650
	% (n+/N)	0.1	1.6	0.6	3.0	1.0	1.8	0.3
h1618	n+	4384	1619	54	2055	308	729	9 149
	% (n+/N)	1.9	20.9	11.7	27.0	43.8	55	3.7
hr other types	n+	10 032	3 101	53	3 622	282	506	17 596
	% (n+/N)	4.4	40.0	11.4	47.6	40.1	38.2	7.2

** hrHPV present at the exception of HPV16 or HPV18.*

Important data can be derived from this cyto-virological matrix with respect to the burden of follow-up of hrHPV+ women to be followed-up according to different triage algorithms using HPV genotyping and reflex cytolology.

Let us assume that all hrHP+ women (10.9% of the screening population age 25-64 years) are triaged by cytology, then 46.1% would have to be referred. If also the HPV1618 testing would be proposed to hrHPV+ women with normal cytology, then 17.8% of hrHPV+ women would be added to referral or 62.5% of all hrHPV+ women.

If at the first triage step HPV1618 genotyping should be performed, then 34.2% of hrHPV+ women would need referral.

6.3.5 Influence of age

6.3.5.1 Variation of the prevalence of cytological abnormalities by age

The variation in prevalence of cytological cervical lesions by age is shown in Table 37 (by 10-year age group) and Figure 39 (by 5-year age group). ASC-US and LSIL peak in the age-group 20-24 years and decrease progressively thereafter. ASC-H and HSIL peak at 25-34 years whereas AGC progressively reaches a maximum in the age range 45-49 (Figure 40). Prevalences at the age >70 are unstable.

Table 37 – Prevalence of unsatisfactory cytology, normal cytology, ASC-US, AGC, LSIL, ASC-H and HSIL+ by 10-year age group (restricted to period >28 June 2009, screening group)

Age (years)	n+ %	Cytological categories							Total
		Unsatisfactory	NILM	ASC-US	AGC	LSIL	ASC-H	HSIL	
10-19	n+	3	7 518	358	1	598	11	23	8 512
	% (n+/N)	0.04	88.32	4.21	0.01	7.03	0.13	0.27	100
20-29	n+	32	49 379	3 021	39	4 197	252	409	57 329
	% (n+/N)	0.06	86.13	5.27	0.07	7.32	0.44	0.71	100
30-39	n+	58	62 745	2 374	112	2 580	225	506	68 600
	% (n+/N)	0.08	91.47	3.46	0.16	3.76	0.33	0.74	100
40-49	n+	56	67 732	2 142	189	1 972	168	339	72 598
	% (n+/N)	0.08	93.3	2.95	0.26	2.72	0.23	0.47	100
50-59	n+	69	51 342	1 322	114	876	114	177	54 014
	% (n+/N)	0.13	95.05	2.45	0.21	1.62	0.21	0.33	100
60-69	n+	56	26 751	524	47	289	51	63	27 781
	% (n+/N)	0.2	96.29	1.89	0.17	1.04	0.18	0.23	100
70-79	n+	27	8 093	135	32	66	16	23	8 392
	% (n+/N)	0.32	96.44	1.61	0.38	0.79	0.19	0.27	100

80-89	n+	8	1 100	26	12	12	1	5	1 164
	% (n+/N)	0.69	94.5	2.23	1.03	1.03	0.09	0.43	100
90-99	n+	0	39	1	1	0	0	0	41
	% (n+/N)	0	95.12	2.44	2.44	0	0	0	100
Total	n+	309	274 699	9 903	547	10 590	838	1 545	298 431
	% (n+/N)	0.1	92.05	3.32	0.18	3.55	0.28	0.52	100

Figure 39 – Prevalence of cytological abnormalities by 5-year age group

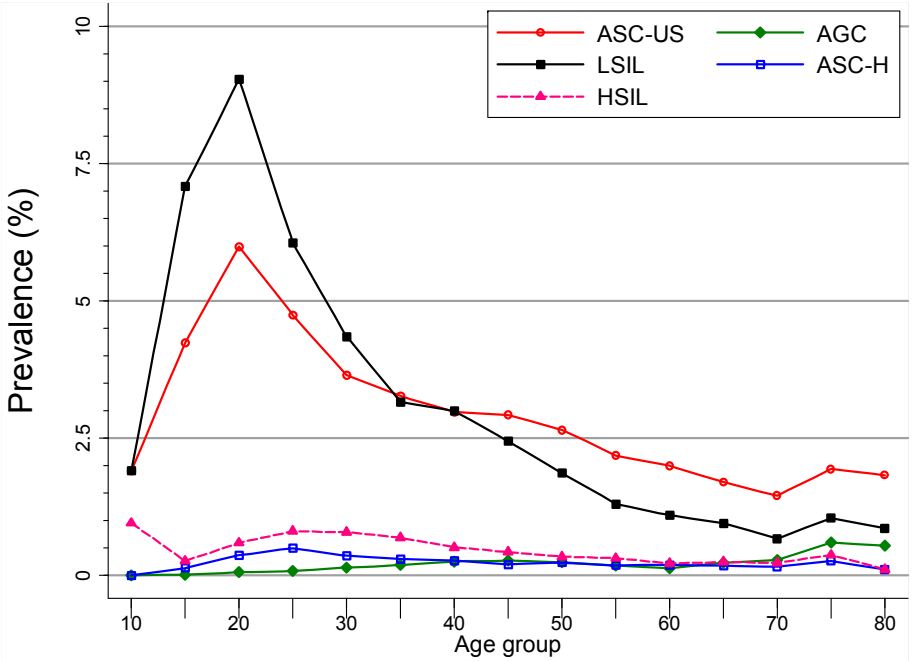
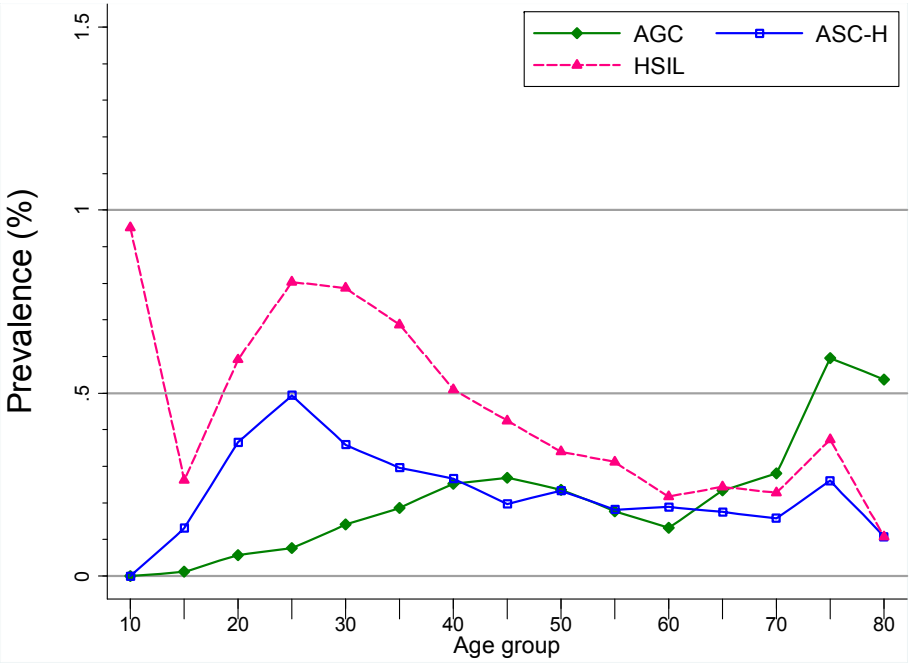


Figure 40 – Prevalence of AGC, ASC-H and HSIL by 5-year age group



6.3.5.2 *Variation of the prevalence of HPV infection by age*

The prevalence of hrHPV infection reaches a peak in the age group 20-24 (19%) and then decreases progressively with increasing age up to age group 60-64 (6%) (see Figure 41). After that age, the prevalence remains a rather stable.

Figure 41 – Prevalence of high-risk HPV infection by age (red full line, with 95% CI in blue interrupted line) (women screened after 28 June 2009)

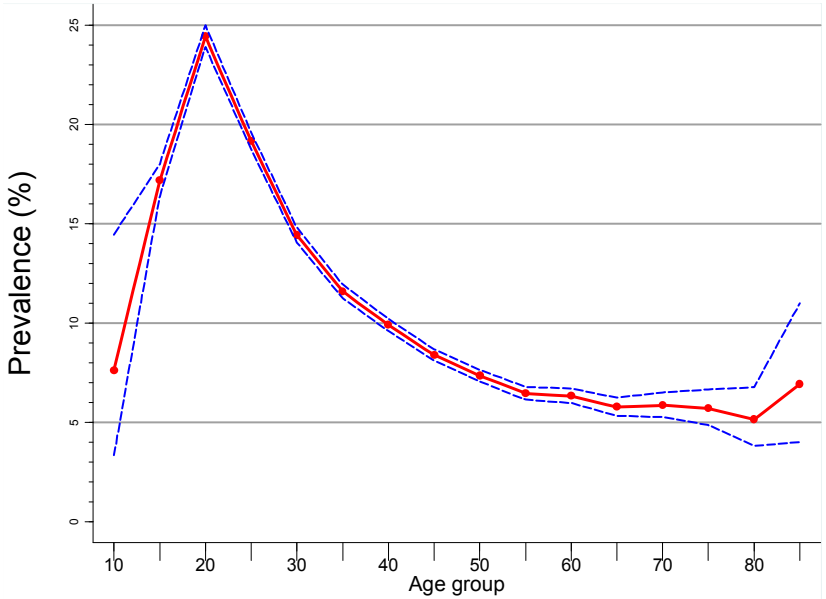
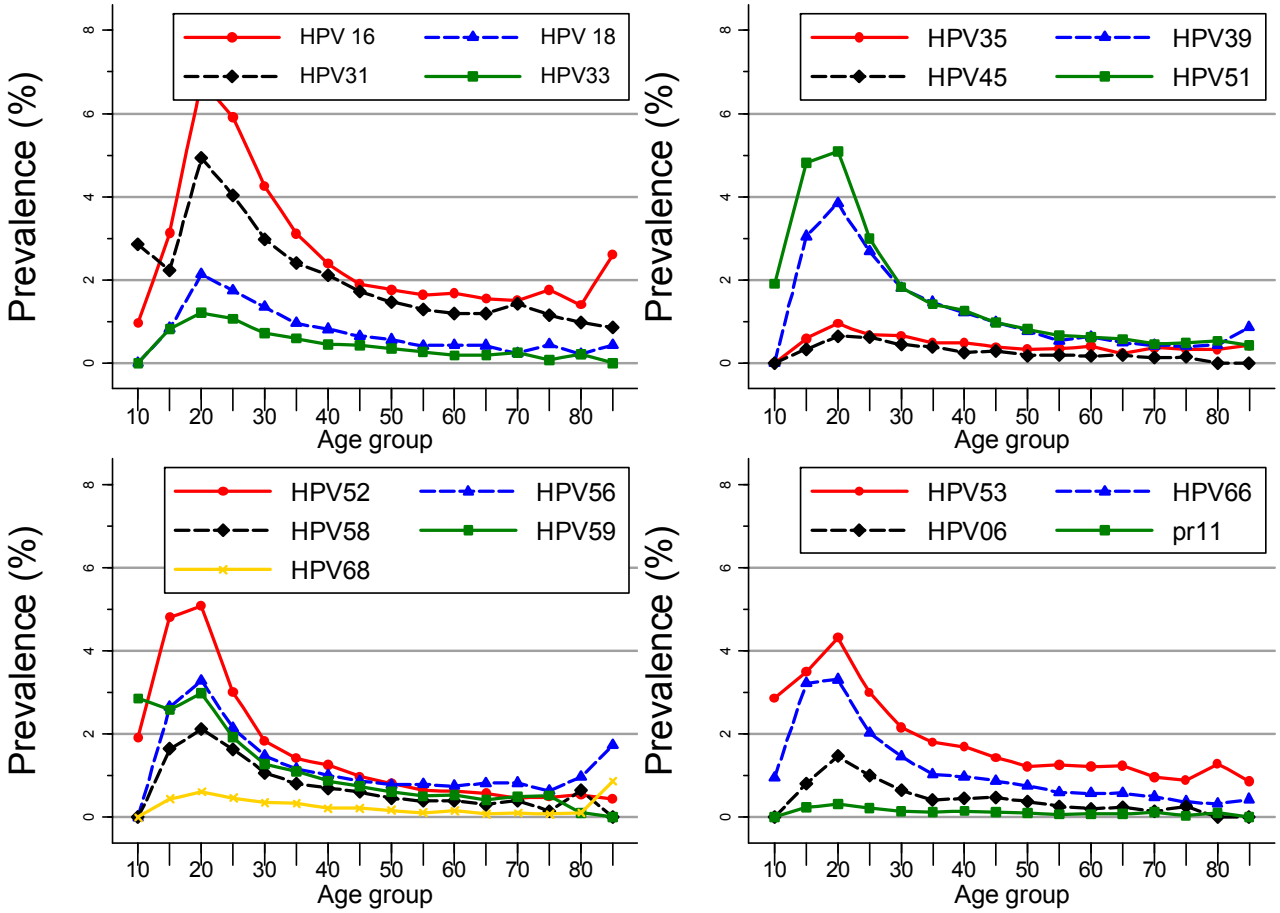


Table 38 shows the age-specific prevalence for hrHPV and for a selection of types included in prophylactic vaccines. Figure 42 shows the variation by age for all the 17 assessed HPV genotypes. The type-specific curves show the same age patterns as for hrHPV infection.

Table 38 – Prevalence of high-risk HPV infection and infection with certain HPV types included in vaccines, by 5-year age group

Age group	N	hrHPV	HPV16	HPV1618	HPV6	HPV11
10-14	105	7.6%	1.0%	1.0%	0.0%	0.0%
15-19	8402	17.2%	3.1%	3.7%	0.8%	0.2%
20-24	24330	24.4%	6.8%	8.5%	1.5%	0.3%
25-29	32960	19.2%	5.9%	7.3%	1.0%	0.2%
30-34	34801	14.4%	4.2%	5.4%	0.7%	0.1%
35-39	33739	11.6%	3.1%	3.9%	0.4%	0.1%
40-44	36057	9.9%	2.4%	3.1%	0.5%	0.2%
45-49	36467	8.4%	1.9%	2.5%	0.5%	0.1%
50-54	30897	7.4%	1.8%	2.3%	0.4%	0.1%
55-59	23053	6.5%	1.6%	2.0%	0.3%	0.1%
60-64	17489	6.3%	1.7%	2.1%	0.2%	0.1%
65-69	10247	5.8%	1.6%	1.9%	0.2%	0.1%
70-74	5696	5.9%	1.5%	1.7%	0.1%	0.1%
75-79	2679	5.7%	1.8%	2.2%	0.3%	0.0%
80-84	932	5.2%	1.4%	1.6%	0.0%	0.1%
85-89	231	6.9%	2.6%	3.0%	0.0%	0.0%

Figure 42 – Age-specific prevalence of infection with individual HPV types



6.3.6 *Single and multiple high-risk HPV infections*

Below, we stratify data by the presence of single or multiple infections. The analysis is restricted to infection with high-risk types. Only cases screened after 28 June 2009 with amplifyable DNA are included. Most infected women carried one single HPV type (8.6%). In 73% of samples with an hrHPV infection contained only a single HPV type was identified and in 27% multiple types were detected. The frequency of more types in one sample decreased with the number concurrent types (see Table 39). Ten women had seven, three women had eight and one woman had nine infections.

Table 39 – Frequency of cervical infections with no, single or multiple high-risk HPV types

Nb of hr types	n	% of all screened	% among women with hrHPV
0	263 129	88.15	-
1	25 793	8.64	72.9%
2	6631	2.22	18.7%
3	2054	0.69	5.8%
4	602	0.2	1.7%
5	222	0.07	0.6%
6	62	0.02	0.2%
7	10	0	0.028%
8	3	0	0.008%
9	1	0	0.003%
Total	298 507	100	

The distribution of types in 25 793 women with one single high-risk type is shown in Table 40.

.

Table 40 – Distribution of types in cases with one single high-risk infection

Types	n	%
16	5797	22.48
18	1451	5.63
31	4175	16.19
33	848	3.29
35	819	3.18
39	2068	8.02
45	514	1.99
51	2676	10.37
52	2180	8.45
56	2094	8.12
58	1285	4.98
59	1654	6.41
68	232	0.9
Total	25 793	100

HPV16 was the most common type in single, double and triple or more infections. HPV31 was the second most frequent type in single and multiple infections. However, the relative contribution of both types was lower in multiple compared to single infections. HPV51 was the third most frequent type in single and double infections but only the fourth in triple or higher-degree multiple infections were the 3rd place was taken by HPV39 (Table 41 and Table 42).

Table 41 – Frequency of high-risk HPV types in single, double, triple, quadruple, quintuple and sextuple infections

	Number of infections per specimen							
HPV type	**Single**		**Double**		**≥ Triple**		**Total**	
16	5 797	22.5%	2 224	16.8%	1469	14.5%	9 490	19.3%
18	1 451	5.6%	804	6.1%	655	6.5%	2 910	5.9%
31	4 175	16.2%	1 763	13.3%	1237	12.2%	7 175	14.6%
33	848	3.3%	470	3.5%	411	4.0%	1 729	3.5%
35	819	3.2%	401	3.0%	300	3.0%	1 520	3.1%
39	2 068	8.0%	1 402	10.6%	1097	10.8%	4 567	9.3%
45	514	2.0%	281	2.1%	244	2.4%	1 039	2.1%
51	2 676	10.4%	1 432	10.8%	1080	10.6%	5 188	10.5%
52	2 180	8.5%	1 283	9.7%	1066	10.5%	4 529	9.2%
56	2 094	8.1%	1 111	8.4%	843	8.3%	4 048	8.2%
58	1 285	5.0%	777	5.9%	621	6.1%	2 683	5.5%
59	1 654	6.4%	987	7.4%	833	8.2%	3 474	7.1%
68	232	0.9%	327	2.5%	299	2.9%	858	1.7%
Total infections	25 793	100.0%	13 262	100.0%	10 155	100.0%	49 210	100.0%

Table 42 – Ranking of high-risk HPV types by frequency in single, double and triple higher degree multiple infections

	Single		Double		≥Triple	
Rank	**Type**	**%**	**Type**	**%**	**Type**	**%**
1	16	22.5%	16	16.8%	16	14.5%
2	31	16.2%	31	13.3%	31	12.2%
3	51	10.4%	51	10.8%	39	10.8%
4	52	8.5%	39	10.6%	51	10.6%
5	56	8.1%	52	9.7%	52	10.5%
6	39	8.0%	56	8.4%	56	8.3%
7	59	6.4%	59	7.4%	59	8.2%
8	18	5.6%	18	6.1%	18	6.5%
9	58	5.0%	58	5.9%	58	6.1%
10	33	3.3%	33	3.5%	33	4.0%
11	35	3.2%	35	3.0%	35	3.0%
12	45	2.0%	68	2.5%	68	2.9%
13	68	0.9%	45	2.1%	45	2.4%

6.3.7 Geographical distribution of high-risk HPV infection

The geographic variation in the prevalence of hrHPV among screened women aged 25-64, is shown in Table 43 (by province) and Figure 43 (and Table 44) (by arrondissement). Prevalences were adjusted for age using truncated direct standardization with European reference population. At provincial level, the amplitude of variation was limited: the standardized prevalences fluctuated between 10% (West- and East Flanders, Flemish-Brabant) and 14% (Luxembourg). At district level, the variation was larger: 0% (Bastogne) and 37% (Arlon). However, these extreme values might be caused by selection bias and random variation due to the small numbers. When we include only districts with at least 100 women, the prevalence is between 8% (Diksmuide) and 18% (Oudenaarde).

Table 43 – Crude and age-standardised prevalence of high-risk HPV infection, by province

			crude prevalence			age-standardised prevalence		
Province	N	n+	%+	lo	up	%+	lo	up
Antwerpen	120 236	13 723	11.4%	11.2%	11.6%	11.0%	10.8%	11.2%
W-Vlaanderen	42 269	4049	9.6%	9.3%	9.9%	9.7%	9.4%	10.0%
O-Vlaanderen	38 347	3695	9.6%	9.3%	9.9%	9.7%	9.4%	10.0%
Hainaut	2358	288	12.2%	10.9%	13.5%	12.8%	11.4%	14.2%
Liège	216	27	12.5%	8.1%	16.9%	12.0%	8.0%	17.1%
Limburg	12 763	1393	10.9%	10.4%	11.5%	11.6%	11.1%	12.2%
Luxembourg	78	11	14.1%	6.4%	21.8%	15.2%	8.2%	25.3%
Namur	207	24	11.6%	7.2%	16.0%	11.6%	7.6%	16.8%
Vlaams-Brabant	14 191	1456	10.3%	9.8%	10.8%	10.4%	9.9%	10.9%
Brussels	12 056	1730	14.3%	13.7%	15.0%	12.8%	12.2%	13.4%
Brabant-Wallon	1064	112	10.5%	8.7%	12.4%	10.2%	8.5%	12.2%
Total	243 785	26 508	10.9%	10.7%	11.0%			

** Directly standardized prevalence computed using the European standard population.*

Figure 43 – Prevalence of high-risk HPV infection, by district (age-standardised using the European reference population)

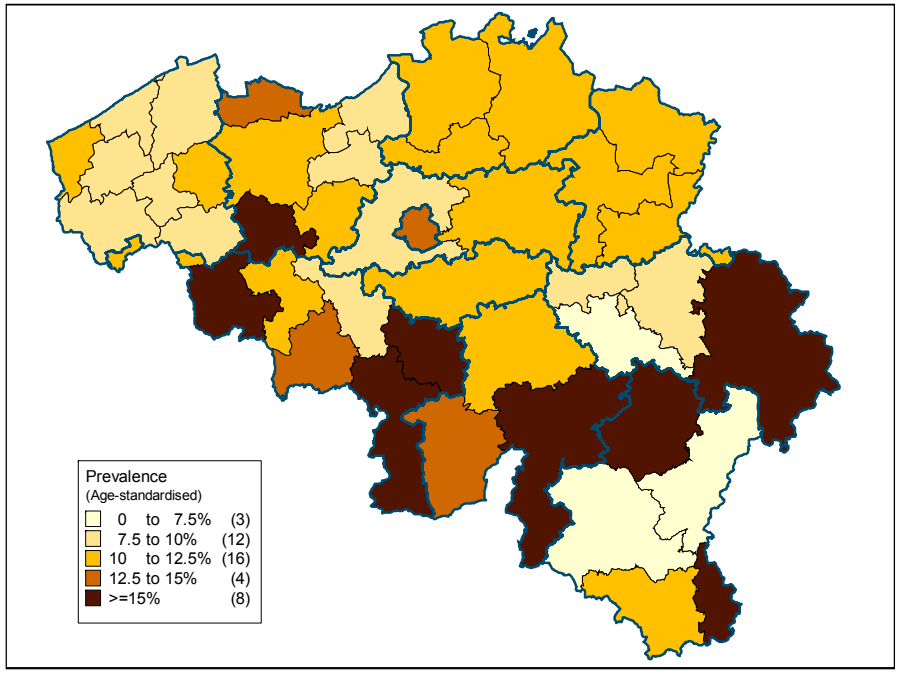


Table 44 – Prevalence (crude and age-standardised) of hrHPV infection among screened women (by district, ranked by increasing prevalence)

				Crude prevalence			Age-standardised prevalence		
NIS	Arrondissement	N	n+	%+	lower CI	upper CI	%+	lower CI	upper CI
82	Bastogne	9	0	0.0%	0.0%	33.6%	0.0%	0.0%	33.6%
61	Huy	22	1	4.5%	0.0%	13.2%	2.1%	0.0%	15.4%
84	Neufchâteau	22	1	4.5%	0.0%	13.2%	4.9%	0.1%	22.8%
32	Disksmuide	3 027	258	8.5%	7.5%	9.5%	8.2%	7.3%	9.3%
33	Ieper	245	21	8.6%	5.1%	12.1%	8.9%	5.7%	13.3%
36	Roeselare	1 324	125	9.4%	7.9%	11.0%	8.9%	7.4%	10.6%
46	St-Niklaas	24 363	2 317	9.5%	9.1%	9.9%	9.2%	8.8%	9.5%
62	Liège	79	9	11.4%	4.4%	18.4%	9.3%	3.6%	17.4%
55	Soignies	190	20	10.5%	6.2%	14.9%	9.3%	5.7%	14.6%
31	Brugge	12 379	1 137	9.2%	8.7%	9.7%	9.5%	8.9%	10.0%
34	Kortrijk	4 896	477	9.7%	8.9%	10.6%	9.7%	8.8%	10.5%
23	Vilvoorde	8 730	846	9.7%	9.1%	10.3%	9.7%	9.1%	10.3%
64	Waremmes	50	6	12.0%	3.0%	21.0%	9.7%	3.3%	21.8%
35	Oostende	14 515	1 417	9.8%	9.3%	10.2%	9.9%	9.4%	10.4%
42	Dendermonde	6 816	620	9.1%	8.4%	9.8%	10.0%	9.3%	10.7%
25	Walloon-Brabant	1 064	112	10.5%	8.7%	12.4%	10.2%	8.5%	12.2%
13	Turnhout	10 811	1 136	10.5%	9.9%	11.1%	10.4%	9.8%	11.0%
37	Tielt	606	68	11.2%	8.7%	13.7%	10.6%	8.2%	13.3%
38	Veurne	5 277	546	10.3%	9.5%	11.2%	10.7%	9.9%	11.6%
92	Namur	123	14	11.4%	5.8%	17.0%	10.9%	5.7%	17.4%
73	Tongeren	3 965	395	10.0%	9.0%	10.9%	10.9%	9.9%	11.9%
11	Antwerpen	96 590	11 193	11.6%	11.4%	11.8%	11.0%	10.8%	11.2%
12	Mechelen	12 835	1 394	10.9%	10.3%	11.4%	11.1%	10.6%	11.7%
51	Ath	49	5	10.2%	1.7%	18.7%	11.2%	3.4%	22.2%

41	Aalst	5 102	492	9.6%	8.8%	10.5%	11.2%	10.4%	12.1%
85	Virton	15	2	13.3%	0.0%	30.5%	11.3%	1.7%	40.5%
54	Mouscron	1 165	115	9.9%	8.2%	11.6%	11.5%	9.7%	13.5%
72	Maaseik	3 165	342	10.8%	9.7%	11.9%	11.6%	10.5%	12.7%
24	Leuven	5 461	610	11.2%	10.3%	12.0%	11.6%	10.8%	12.5%
44	Gent	1 671	211	12.6%	11.0%	14.2%	12.0%	10.5%	13.6%
71	Hasselt	5 633	656	11.6%	10.8%	12.5%	12.1%	11.2%	12.9%
93	Phillipeville	50	7	14.0%	4.4%	23.6%	12.7%	4.5%	24.3%
21	Brussels	12 056	1 730	14.3%	13.7%	15.0%	12.8%	12.2%	13.4%
43	Eeklo	264	31	11.7%	7.9%	15.6%	12.8%	9.1%	17.5%
53	Mons	32	5	15.6%	3.0%	28.2%	14.2%	5.3%	32.8%
52	Charleroi	585	91	15.6%	12.6%	18.5%	15.1%	12.2%	18.2%
56	Thuin	75	13	17.3%	8.8%	25.9%	15.5%	8.6%	26.3%
57	Tournai	262	39	14.9%	10.6%	19.2%	15.6%	11.5%	20.6%
45	Oudenaarde	131	24	18.3%	11.7%	24.9%	17.5%	11.5%	25.2%
91	Dinant	34	3	8.8%	0.0%	18.4%	17.7%	6.8%	34.5%
63	Verviers	65	11	16.9%	7.8%	26.0%	18.2%	9.9%	30.0%
83	Marche-en-Famenne	24	5	20.8%	4.6%	37.1%	23.6%	9.8%	46.7%
81	Arlon	8	3	37.5%	4.0%	71.0%	37.50%	8.5%	75.5%

6.3.8 *Risk of cytological abnormalities associated with presence of human papillomavirus types*

In Table 45, we show the relative risk or risk ratio (RR) for a cytological diagnosis of HSIL or AIS or worse associated with a HPV infection (13 high-risk types, individual types). This table also contains the prevalence of HPV infection. From, the relative risk we have computed the attributable risk among infected women [AR_{exp}=(RR-1)/RR] and the lower and upper 95% confidence interval bound[d]. From the relative risk and the prevalence of HPV infection we have computed the attributable risk in the study population [AP_{pop}=p(RR-1)/(p(RR-1)+1)].

[d] AE_{exp}= equivalent to vaccine efficacy. It represents the reduction in vaccine-type associated HSIL+ lesions if infection with that type is eliminated by a 100% effective prophylactic vaccine assuming absence of cross-protection.

Table 45 – Risk ratio of a cytological result of HSIL or adenocarcinoma associated with presence of HPV type(s); prevalence of HPV in the study population, attributed risk (AR_{exp}) among women with a given HPV infection and in the study population (AR_{pop})

Type(s)	Risk ratio	RR (lcib)	RR(ucib)	Prevalence type	ARexp (*)	ARexp (licb)	Arexp (ucib)	ARpop
hrHPV	106.4	87.0	130.2	10.9%	99.1%	98.9%	99.2%	92.0%
HPV06	4.8	3.6	6.5	0.5%	79.3%	71.9%	84.7%	1.9%
HPV11	4.9	2.7	8.7	0.1%	79.4%	63.0%	88.5%	0.5%
HPV16	27.8	25.2	30.7	2.9%	96.4%	96.0%	96.7%	44.1%
HPV18	11.4	9.7	13.4	0.9%	91.2%	89.7%	92.5%	8.7%
HPV31	8.1	7.1	9.2	2.2%	87.6%	85.8%	89.1%	13.7%
HPV33	16.7	14.1	19.8	0.5%	94.0%	92.9%	94.9%	7.8%
HPV35	8.7	6.8	11.1	0.5%	88.5%	85.4%	91.0%	3.6%
HPV39	6.8	5.7	8.0	1.3%	85.2%	82.5%	87.5%	7.1%
HPV45	7.8	5.8	10.6	0.3%	87.2%	82.6%	90.5%	2.2%
HPV51	8.5	7.4	9.9	1.4%	88.3%	86.5%	89.9%	9.5%
HPV52	11.5	10.1	13.2	1.3%	91.3%	90.1%	92.4%	12.3%
HPV53	5.1	4.3	6.1	1.8%	80.5%	76.9%	83.5%	6.8%
HPV56	6.3	5.2	7.5	1.2%	84.1%	80.9%	86.7%	5.8%
HPV58	11.7	9.9	13.8	0.8%	91.4%	89.9%	92.7%	7.8%
HPV59	5.6	4.6	6.9	1.0%	82.2%	78.2%	85.5%	4.4%
HPV66	5.7	4.7	6.9	1.1%	82.4%	78.6%	85.5%	4.8%
HPV68	6.2	4.2	9.0	0.3%	83.8%	76.4%	88.8%	1.3%

All tested HPV types were associated with a significantly increased risk of HSIL+ compared to women who did not carry that particular type(s). The type-specific relative risks are lower than usually reported in the literature since the reference group is here the population without infection with a particular type. In case-control studies reported in the literature, the reference group usually is the population without any HPV infection. If we apply this principle on our study population, we obtain the following RR for HPV16: 303.5 (95% CI: 236.13-390.1). This means that a woman infected with HPV16 has a risk for having HSIL which is 303 times higher than a woman who has no detectable HPV.

The HPV types associated with the highest population attributable risk are HPV16 (44%), HPV31 (14%) and HPV52 (12%). The proportion of HSIL associated with HPV18 is 9%.

In Table 46, we compute the relative and attributable risks for different cytological abnormalities associated with HPV16 or HPV18, HPV06-11-16-18 or HPV06-11-16-18-31-33-45-52-58.

Table 46 – Risk of cytological abnormalities associated with HPV16 or HPV18 infection or other combinations of HPV types included in current or future prophylactic vaccines (relative risk and attributable risk among HPV16/18 infected women and in the total study population)

Lesion	Risk ratio	RR (lcib)	RR(ucib)	Prevalence type	ARexp	ARexp (licb)	ARexp (ucib)	ARpop
Risk associated with HPV16 infection								
ASC-US	6.5	6.2	6.8	2.9%	84.5%	83.8%	85.2%	13.9%
AGC	2.2	1.6	3.1	2.9%	55.4%	37.7%	68.0%	3.5%
LSIL	8.5	8.1	8.8	2.9%	88.2%	87.7%	88.7%	18.0%
ASC-H	19.5	17.0	22.4	2.9%	94.9%	94.1%	95.5%	35.3%
HSIL+	27.8	25.2	30.7	2.9%	96.4%	96.0%	96.7%	44.1%
risk associated with HPV16 or 18 infection								
ASC-US	6.7	6.4	7.0	3.7%	85.0%	84.3%	85.7%	17.4%
AGC	2.9	2.2	3.7	3.7%	64.9%	54.0%	73.3%	6.4%
LSIL	8.9	8.6	9.3	3.7%	88.8%	88.3%	89.2%	22.7%
ASC-H	19.9	17.4	22.7	3.7%	95.0%	94.2%	95.6%	41.2%
HSIL+	28.9	26.2	31.9	3.7%	96.5%	96.2%	96.9%	50.9%
risk associated with HPV06, 11, 16 or 18 infection								
ASC-US	7.0	6.7	7.3	4.5%	85.7%	85.0%	86.3%	21.1%
AGC	2.9	2.3	3.8	4.5%	66.0%	55.9%	73.7%	8.0%
LSIL	9.7	9.4	10.1	4.5%	89.7%	89.3%	90.1%	28.0%

ASC-H	19.2	16.8	22.0	4.5%	94.8%	94.1%	95.5%	44.9%
HSIL+	27.2	24.6	30.0	4.5%	96.3%	95.9%	96.7%	53.8%
risk associated with HPV06, 11, 16, 18, 31, 33, 45, 52 or 58 infection								
ASC-US	10.1	9.8	10.5	8.6%	90.1%	89.8%	90.5%	43.9%
AGC	2.4	2.0	3.0	8.6%	58.8%	48.9%	66.9%	10.9%
LSIL	13.7	13.3	14.3	8.6%	92.7%	92.5%	93.0%	52.2%
ASC-H	30.3	26.0	35.3	8.6%	96.7%	96.1%	97.2%	71.5%
HSIL+	49.8	43.8	56.8	8.6%	98.0%	97.7%	98.2%	80.7%

We estimated that by preventing HPV16 and HPV18 infection, the prevalence of ASC-US would decrease with 17%, AGC with 6%, LSIL with 23%, ASC-H with 41% and HSIL with 51%. By preventing also HPV06 and HPV11, the prevalence of these lesions would decrease with a few percentage more. However, elimination of 9 HPV types (HPV06, 11, 16, 18, 31, 33, 45, 52 and 58) would be associated with a substantially greater decrease in occurrence of cytological lesions: 44% (ASC-US), AGC (11%), LSIL (52%), ASC-H (72%) and HSIL (81%).

6.3.9 Relation between occurrence of cytological lesions and presence of single or multiple HPV infections

Table 47 shows the association between the number of concurrent high-risk types and frequency of cytological lesions. A statistically significant positive trend is observed with more frequent severe abnormalities when women are infected with more HPV types (trend test <0.001).

Table 47 – Relation between the number of concurrent high-risk HPV types and occurrence of cytological lesions

Number of types		ASC-US	AGC	LSIL	ASC-H	HSIL	Total
0	n	3621	430	2472	127	101	6751
	%+	53.6	6.4	36.6	1.9	1.5	100.0
1	n+	4384	89	4535	476	885	10369
	%+	42.3	0.9	43.7	4.6	8.5	100.0
2	n+	1360	23	2194	163	335	4075
	%+	33.4	0.6	53.8	4.0	8.2	100.0
3	n+	402	4	929	50	131	1516
	%+	26.5	0.3	61.3	3.3	8.6	100.0
4	n+	110	1	304	14	60	489

	%+	22.5	0.2	62.2	2.9	12.3	100.0
>=5	n+	44	0	183	10	34	271
	%+	16.2	0.0	67.5	3.7	12.5	100.0
Total	n+	9921	547	10617	840	1546	23471
	%+	42.3%	2.3%	45.2%	3.6%	6.6%	100.0%

Trend test:z=281.73 for 6df, p<0.001.

6.3.10 *Multivariate analysis of the risk for HSIL+ associated with HPV types and other factors*

We used a logistic regression model to assess the risk for HSIL+ depending on infection with one or more HPV types, age group, residence (province) and reason for the collection of the specimen (screening or follow-up). Only records with collection date after 28 June 2009 were used. Table 48 shows the results of the logistic regression including all categories for the variables HPV type, age group, reason for specimen collection and province, whereas Table 49 shows the results of a stepwise logistic regression containing only the categories which statistically significant associations.

All hrHPV types but none of the intermediate (53, 66) or low-risk risk types (6, 11) were significantly associated with HSIL. HPV16 showed the highest OR (9.75; 95% CI: 9.06-10.49).

Women in the age groups 30-59 had higher risks than the reference (women aged 20-29 years).

Women in the follow-groups had a higher chance of having HSIL (OR= 2.50; 95% CI: 2.33-2.69).

Women from West-Flanders had a significantly lower risk than the reference group (Antwerp): OR=0.88 (95% CI: 0.80-0.98).

Table 48 – Odds ratios computed by multivariate logistic regression describing the strength of association between occurrence of HSIL and risk factors (infection with one or more HPV genotypes), age group, reason for the collection (screening or follow-up) and province

Risk factor	OR	Std. Err.	z	P>z	95% lcib	95% ucib
Ref= no hrHPV infection						
HPV06	1.02	0.1160	0.14	0.888	0.81	1.27
HPV11	0.75	0.1647	-1.32	0.188	0.49	1.15
HPV16	9.78	0.3661	60.94	0.000	9.09	10.53
HPV18	2.44	0.1576	13.86	0.000	2.15	2.77
HPV31	2.11	0.1027	15.30	0.000	1.92	2.32
HPV33	3.78	0.2577	19.49	0.000	3.31	4.32
HPV35	2.74	0.2508	11.02	0.000	2.29	3.28
HPV39	1.22	0.0825	2.88	0.004	1.06	1.39
HPV45	1.68	0.1994	4.40	0.000	1.33	2.12
HPV51	2.05	0.1163	12.69	0.000	1.84	2.29
HPV52	1.93	0.1103	11.54	0.000	1.73	2.16
HPV53	0.96	0.0614	-0.58	0.563	0.85	1.09

HPV56	1.29	0.0899	3.71	0.000	1.13	1.48
HPV58	2.65	0.1731	14.94	0.000	2.33	3.01
HPV59	1.26	0.0924	3.16	0.002	1.09	1.46
HPV66	1.00	0.0786	-0.05	0.957	0.85	1.16
HPV68	1.35	0.1897	2.15	0.032	1.03	1.78
Ref=age group 20-29						
Age 30-39	1.54	0.0701	9.49	0.000	1.41	1.68
Age 40-49	1.38	0.0713	6.31	0.000	1.25	1.53
Age 50-59	1.24	0.0773	3.48	0.001	1.10	1.40
Age 60-69	0.95	0.0855	-0.55	0.584	0.80	1.14
Age 70-79	1.28	0.1786	1.77	0.077	0.97	1.68
Ref= screening group						
Follow-up	2.51	0.0931	24.84	0.000	2.34	2.70
Ref= Antwerp						
W-Flanders	0.89	0.0468	-2.15	0.032	0.81	0.99
E-Flanders	0.98	0.0491	-0.38	0.702	0.89	1.08
Hainaut	1.14	0.2331	0.65	0.519	0.76	1.70
Liège	0.49	0.3582	-0.97	0.330	0.12	2.05
Limburg	1.08	0.0860	0.96	0.338	0.92	1.26
Namur	0.61	0.4407	-0.69	0.491	0.15	2.52
Fl-Brabant	1.01	0.0748	0.13	0.899	0.87	1.17
Brussels	1.13	0.0834	1.71	0.087	0.98	1.31
Wal-Brabant	0.94	0.2346	-0.24	0.808	0.58	1.53

Table 49 – Odds ratios computed by a stepwise multivariate logistic regression describing the strength of association between occurrence of HSIL and risk factors (infection with one or more HPV genotypes), age group, reason for the collection (screening or follow-up) and province

Risk factor	OR	Std. Err.	z	P>z	95% lcib	95% ucib
Ref= no hrHPV infection						
HPV16	9.75	0.3625	61.24	0.000	9.06	10.49
HPV18	2.44	0.1569	13.89	0.000	2.15	2.77
HPV31	2.10	0.1020	15.32	0.000	1.91	2.31
HPV33	3.76	0.2556	19.50	0.000	3.29	4.30
HPV35	2.72	0.2487	10.94	0.000	2.27	3.25
HPV39	1.21	0.0817	2.80	0.005	1.06	1.38
HPV45	1.68	0.1982	4.36	0.000	1.33	2.11
HPV51	2.05	0.1152	12.73	0.000	1.83	2.29
HPV52	1.92	0.1093	11.50	0.000	1.72	2.15
HPV56	1.29	0.0889	3.67	0.000	1.13	1.47
HPV58	2.64	0.1713	14.90	0.000	2.32	2.99
HPV59	1.25	0.0912	3.05	0.002	1.08	1.44
HPV68	1.36	0.1903	2.17	0.030	1.03	1.79
Ref=age group 20-29						
Age 30-39	1.54	0.0661	10.02	0.000	1.41	1.67
Age 40-49	1.38	0.0673	6.52	0.000	1.25	1.51
Age 50-59	1.23	0.0737	3.47	0.001	1.09	1.38
Ref= screening group						
Follow-up	2.50	0.0925	24.85	0.000	2.33	2.69
Ref= Antwerp						
W-Flanders	0.88	0.0442	-2.46	0.014	0.80	0.98

6.4 Discussion

6.4.1 Strengths

- Enormous data base, probably most extensive cohort with genotyping details.
- Since June 2009: distinction between screening and follow-up is possible.

6.4.2 Weakness

- Only cytological outcome, no viral load data
- Incompleteness of data (lacking follow-up)
- Before June 2009: no distinction between screening and follow-up was possible
- The database is built up according to current clinical use of cervical cytology in combination with HPV testing, as it is currently used. The organization of cervical cancer was mainly opportunistic where respect of screening and management recommendations are often not followed. The database is not built up from a predefined cohort study. Nevertheless associations and natural history questions can be addressed.

6.4.3 Future research

Longitudinal analyses:

- incidence, clearance and persistence of type-specific infection
- incidence of cytological lesions according to baseline virological status
- trend in prevalence of HPV infection, correlated with HPV vaccination status
- completion of database with histological, treatment and vaccination data
- combined analysis with data from the SEHIB study
- linkage with the cancer registry to compete histological data including audit of cancer cases

Preparation of a case-control study including cervical cases and matched with controls involving ~10 large Belgian cyto-pathology laboratories, where the most important exposure factors will be:

- screening versus non-screening (effectiveness of screening in Belgium)
- HPV-enhanced screening (AML/Riatol) versus cytology-based screening (most other laboratories) .
- linkage with data from VALGENT study to estimate expected results when other assays would be used.

7 COMPARISON BELGIUM VERSUS THE NETHERLANDS: USE OF RESOURCES RELATED TO CERVICAL CANCER SCREENING VS. IMPACT

7.1 Introduction

A comparative effectiveness research (CER) will be conducted comparing past, current and future cervical cancer screening activities in Belgium and the Netherlands. Its aim is to describe cervical cancer screening policies and to assess the intensity of screening and follow-up of screen-positive women, including also possible harms and to evaluate differences in the trends in incidence of and mortality from cervical cancer in the two countries.

CER involves the comparison of existing health care interventions to determine which work best and which pose the greatest benefits and harms for patients and health professionals and to assess the circumstances that influence health outcomes. Contrary to randomised clinical trials, CER uses data collected in routine field conditions (Neumann, 2013 NEJM).

The CER will follow methods and use materials used in a recent study comparing the practice of cervical cancer screening in the United States and the Netherlands[141].

From this two-country comparison it was concluded that the intensity in terms of use of Pap smears was fourfold whereas the impact on the mortality from cervical cancer was similar.

Data on the consumption of Pap smears extracted from this study for the Netherlands will be compared with data compiled from the Inter-mutualistic Agency[4, 53].

Previous trend analyses on mortality from cervical cancer in Belgium[142, 143] and Europe[144, 145] will be updated and the pattern of the trends and current burden will be related to the screening intensity[146-149].

7.2 Material and methods

7.2.1 Belgium

The following data sources were used:

- Current burden of incidence of and mortality from cervical cancerEstimates for 2012 for 40 European countries, including Belgium, were requested and received from the International Agency for Research on Cancer (Lyon), corresponding to the GLOBOCAN-2012 estimates described by Ferlay et al for 40 European countries[150]. Previously published bar charts and maps were updated using these GLOBOCAN 20012 estimates[146].
- Trend of mortality from cervical cancer: data from previous trend analyses[142-144] were updated by appending data received from the Directorate General Statistics and Economic Information (DGSEI, formerly known as the National Institute of Statistics, Brussels, Belgium) for the period 1987-2009. There was a gap in availability of data for the period 2000-2002. For these years, mortality rates were estimated by linear interpolation from the two previous and two following years. A correction was made to adjust for deaths from uterine cancer without definition of the topographic origin (cervix uteri or corpus uteri) as explained previously[144]. The trend analysis covered the period 1994 to 2009.
- Incidence of cervical cancer: data on incidence of cervical cancer, published by the Belgian Cancer registry could be derived from *www.kankerregister.org* The trend analysis covered the period 2004 to 2011.
- Screening coverage and intensity of cytological screening:
  - Data on screening coverage (% of women, aged 25-64 years, having had at least one Pap smear in a period) and Pap smear consumption (#smears / #women ratio) were available from reimbursement data for the period 1996-2006 from two published reports based on databases compiled by the Intermutuality Agency (IMA)[4, 53].
  - Data on the total number of reimbursed Pap smears collected and interpreted per year in Belgium were obtained from RIZIV-INAMI

for the periods 1983-2012. These latter data just contain total national numbers without any geographic or demographic detail.

7.2.2 The Netherlands

- Current burden of incidence of and mortality from cervical cancer: as for Belgium, derived from GLOBOCAN2012.
- Trend of mortality from cervical cancer.

  Data from a previous European trend analysis[144] were updated using the WHO mortality database from which data were extracted for the Netherlands up to 2012. A correction was made to adjust for deaths from uterine cancer without definition of the topographic origin (cervix uteri or corpus uteri) as explained previously[144].
- *Incidence of cervical cancer*: data on incidence of cervical cancer were extracted from http://www.cijfersoverkanker.nl/nkr/index. The trend analysis covered the period 1989 to 2011.
- Intensity of cytological screening

  Screening intensity expressed as the number of Pap smears interpreted by 1000 women per year standardized for the US population were derived of a recent publication comparing cervical cancer screening in the USA and the Netherlands[141].

7.3 Results

7.3.1 Burden of cervical cancer in Belgium and the Netherlands

Figure 44 – Incidence of and mortality rates of cervical cancer in the 28 Members States of the European Union, for 2012, sorted by increasing mortality rate (standardised according to the World standard population). The arrow indicate the Netherlands (green) and Belgium (red)

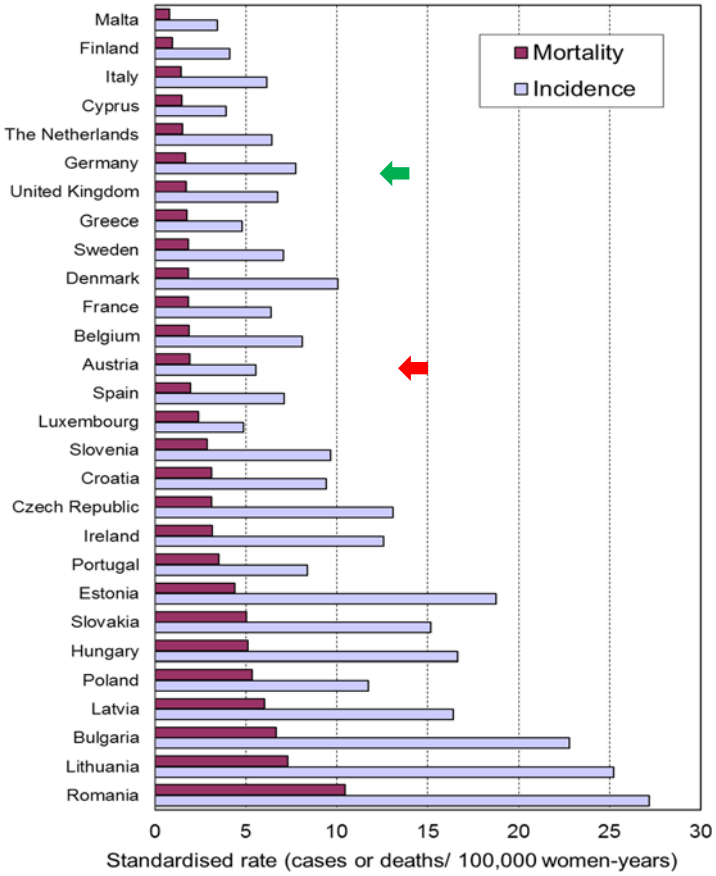


Figure 45 – Geographic distribution of the standardised incidence rate of cervical cancer, in 41 European countries, estimated for 2008 (per 100,000 women-years, standardised using the World reference population). The counts in brackets in the legend correspond to the number of countries in each range

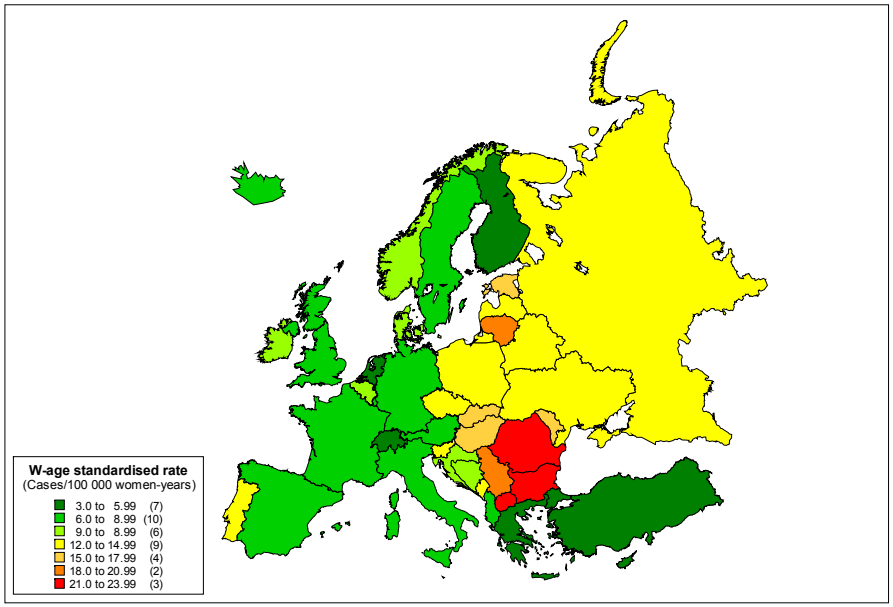


Figure 46 – Geographic distribution of the age-standardised rate of mortality from cervical cancer, in 41 European countries, estimated for 2008 (per 100,000 women-years, standardised using the World reference population). The counts in brackets in the legend correspond to the number of countries in each range

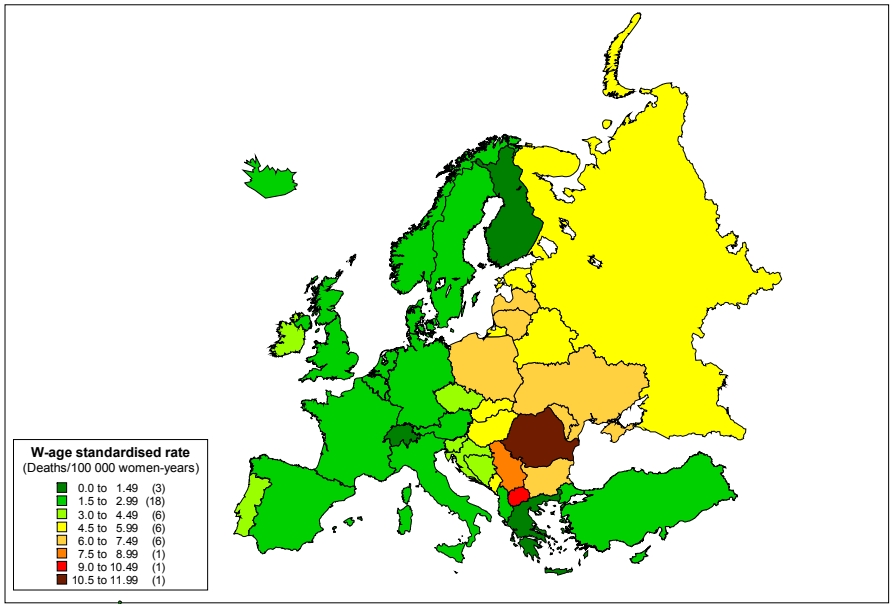
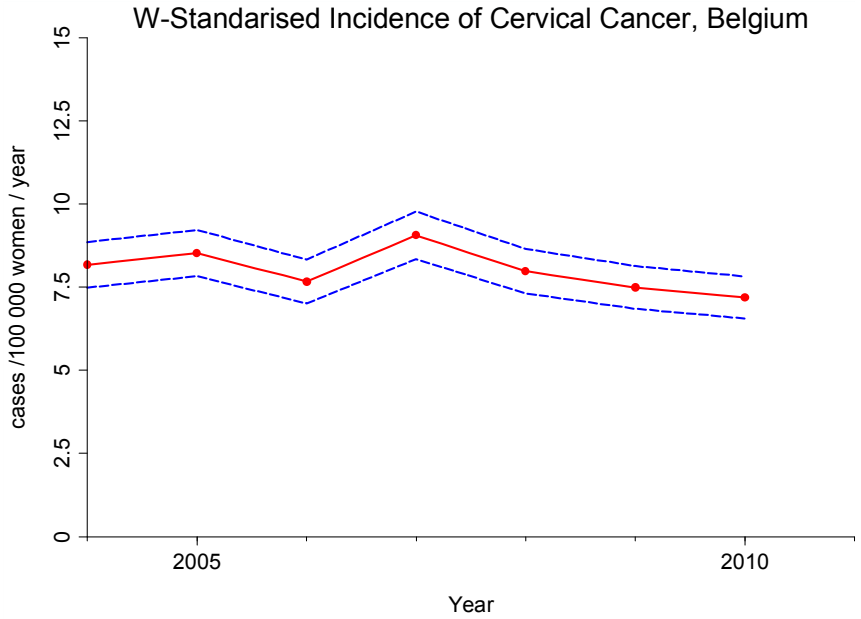


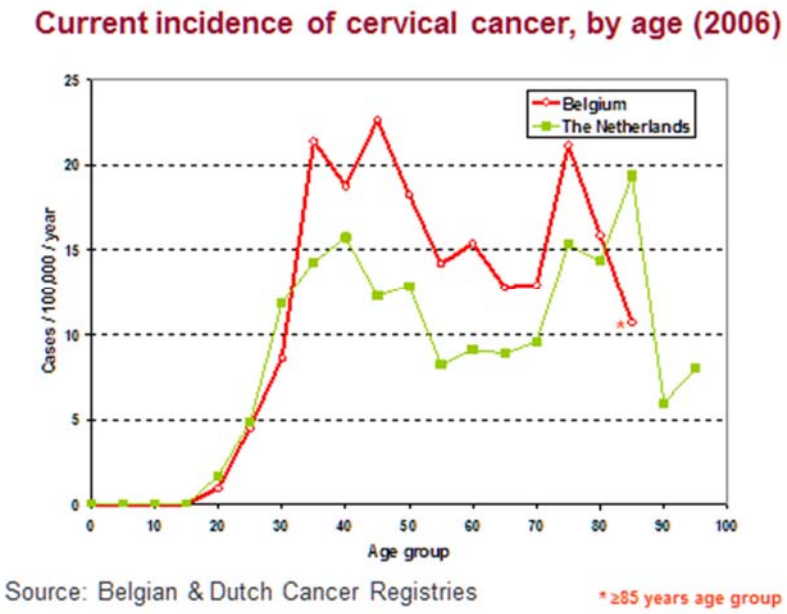
Table 50 – Burden of cervical cancer incidence and mortality, estimated for the year 2012, in Belgium and the Netherlands: number of newly diagnosed cases, crude and age-standardised incidence and mortality rates; and cumulative risk of developing cervical cancer or dying from cervical cancer before the age 75 years. Standardisation was performed using the World (W-ASR) and the European (E-ASR) reference population

Country	Cases (x 100)	Crude rate	W-ASR	E-ASR	Cum rate (%)
Incidence					
Belgium	639	11.62	8.10	10.20	0.61
The Netherlands	750	8.92	6.43	7.98	0.43
Mortality					
Belgium	219	3.98	1.89	2.69	0.19
The Netherlands	242	2.88	1.53	2.14	0.14

7.3.2 Incidence of cervical cancer

Figure 47 – World-age-standardized rate of cervical cancer (ICD-X=C53), cases per 100 000 women-years (Belgium, 2004-2010; Source National Cancer Registry)





7.3.3 *Trend analysis of the mortality from cervical cancer*

Figure 48 – Mortality from cervical cancer in Belgium (1954-2009), standardized for age using the World Reference population after correction for deaths from uterine cancer not otherwise specified

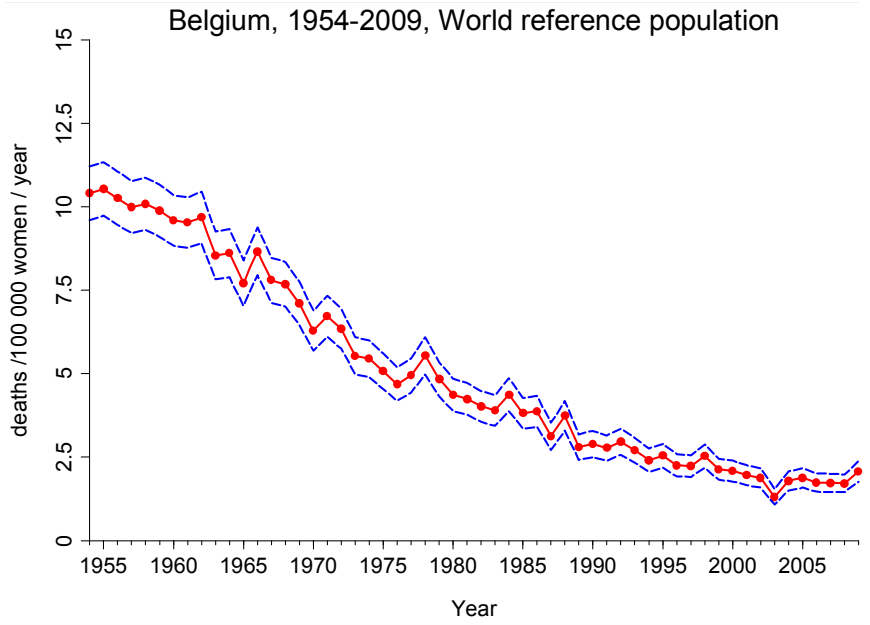
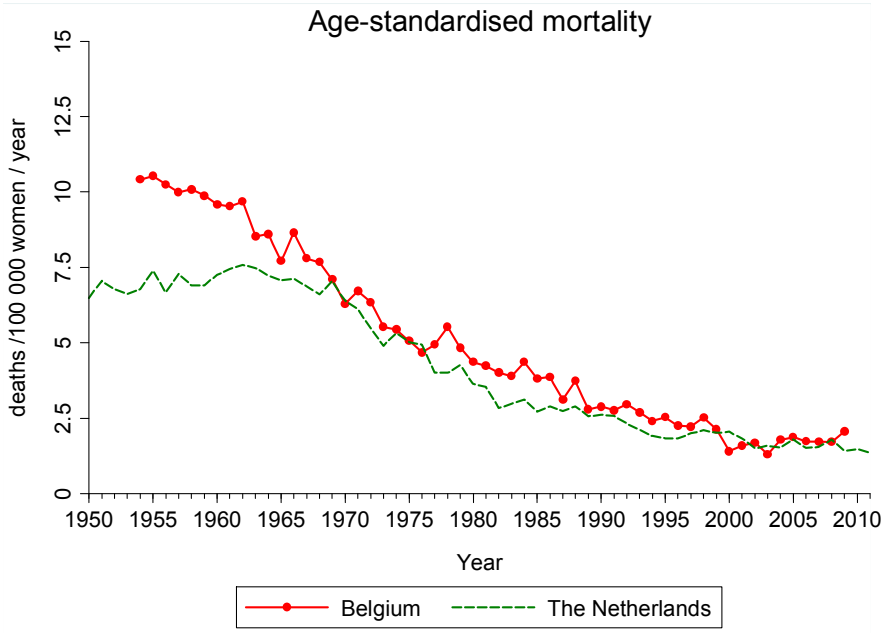


Figure 49 – Mortality from cervical cancer in Belgium (1954-2009) and the Netherlands (1950-2011), standardized for age using the World Reference population after correction for deaths from uterine cancer not otherwise specified



7.3.4 Screening policies

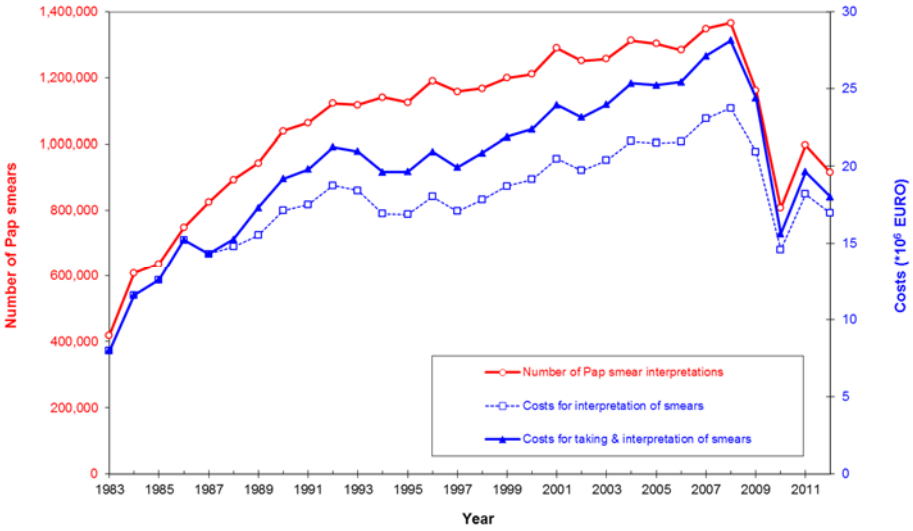
7.3.4.1 Belgium

In the Flemish Community, a policy of three-yearly Pap smears for women aged 25-64 years was adopted in the 1990s in agreement with European guidelines[2]. This policy was recommended by the five Flemish provinces who were in charge of an invitation system where women belonging to the target age group were invited to have a Pap smear taken by their GP or gynaecologist. In a later stage, voluntary cervical cytology registries were set up at provincial level in certain provinces (Limburg[151], Antwerp[2], Flemish-Brabant[2]) and some of them (Antwerp, Flemish-Brabant) were used for targeted invitation (only those without a Pap smear registered over the last three years in the local registry). None of these registries reached complete registration coverage since based on voluntary participation of the laboratories. Different measures were taken to assure the protection of privacy. In the French Community, the same screening policy was adapted but no invitation systems were set up[152].

In spite of the scientific evidence and recommendations to screen once every three years between the age of 25 to 64, this policy was not followed in practice. The main reason was that reimbursement of medical acts (visit to GP or gynaecologist, collection of smear, cytological interpretation) were regulated at the Federal level (RIZIV/INAMI) and were not conditioned by the respect of guidelines. In fact, there was no limitation in reimbursement of the collection and interpretation of a Pap smear and in many gynaecological practices the annual Pap smear continued to be the mainstay. The screening coverage and the amount of over-screening was hardly influenced by the interventions set up by the Flemish provinces.

In the meanwhile, reimbursement conditions in Belgium have changed. Previously, Pap smears were reimbursed without any interval restrictions, but since May 2009, two different types of cervix cytology examinations were distinguished: a) screening (minimum interval of 2 years) and b) follow-up (maximum 2 per year, only after prior abnormal cytology)[153]. A small financial contribution was paid by the individual concerned. The implementation of this regulation has reduced dramatically the total volume of cervical cytology examinations performed: from 1.37 million in 2008 to 0.81 million in 2010, or a reduction of 41% (see Figure 50)[154]. In March 2013, a new Royal Decree was published that restricted reimbursement of screening cytology to once every three years. This three-yearly Pap smear is now completely free of charge[155].

Figure 50 – Annual number of Pap smears interpreted and expenses for reimbursement (in € or € equivalents/year) for collection and interpretation of Pap smears (Belgium, 1983-2012, Source: INAMI/RIZIV)



7.3.4.2 The Netherlands

In 2016, the Netherlands will switch to HPV-based cervical cancer screening (Figure 51).

Test: one validated hrHPV DNA test (choice dependent on an official call for applications addressed to manufacturers of HPV assays).

Triage: double cytology: reflex testing on hrHPV positive women and if negative repeat cytology at 12 months.

All women between 30-60 years will be invited to contact their GP for collection of a specimen. The interval will be 5 years from 30-40 and every 10 years for older women if previous screening tests were hrHPV-negative but continued at 5 years if a positive hrHPV-positive result was found before.

Only 4-6 laboratories will be appointed to perform HPV and cytology testing. Cytology testing will be performed in the same laboratory where HPV testing is done.

Women non responding to the invitation to contact their GP, will receive a self-sampling kit for HPV testing. Women with a hrHPV-positive result on their self-sample will be referred to their GP for collection of sample for cytology triage.

Table 51 – Current policies and other key characteristics of cervical cancer screening in Belgium and the Netherlands

	Belgium	The Netherlands
System	Mainly opportunistic	Fully organised
Target age range	25-64 yrs	30-59 yrs
Interval	3 yrs (in reality often ~yearly)	5 yrs (respected)
Screening test	Conventional or liquid cytology	Conventional or liquid cytology
Funding matched to screening policy	Only since March 2013	Yes, since start of programme
Invitational system	Call-recall Only women not recently screened	Call All women
Health professional collecting sample	Mainly gynaecologists	GPs or their practice assistant
Screening registry	Under construction, well advanced	Operational

7.3.5 *Intensity of screening*

Table 52 – Consumption of Pap smears and one-year screening coverage between 1996 and 2006 for women aged 25 and 64 years old in Belgium[4,53]

Year	Number of women 25-64 years	Number of smears	Number of women screened	1-year coverage	#smears/#women ratio	# smears/ screened woman
1996	2 694 738	873 359	807 018	29.9%	0.32	1.08
1997	2 703 970	915 851	846 669	31.3%	0.34	1.08
1998	2 710 432	975 223	906 196	33.4%	0.36	1.08
1999	2 717 013	996 947	924 987	34.0%	0.37	1.08
2000	2 723 354	1 010 768	930 323	34.2%	0.37	1.09
2002	2 741 601	1 038 028	971 726	35.4%	0.38	1.07
2003	2 755 767	1 043 990	977 596	35.5%	0.38	1.07
2004	2 767 971	1 062 223	993 009	35.9%	0.38	1.07
2005	2 782 136	1 067 024	999 875	35.9%	0.38	1.07
2006	2 806 442	1 065 231	999 747	35.6%	0.38	1.07

Table 53 – Consumption of Pap smears, three-year screening coverage and #smears/#women ratio between 2002 and 2006 for women between 25 and 64 years old (Belgium)

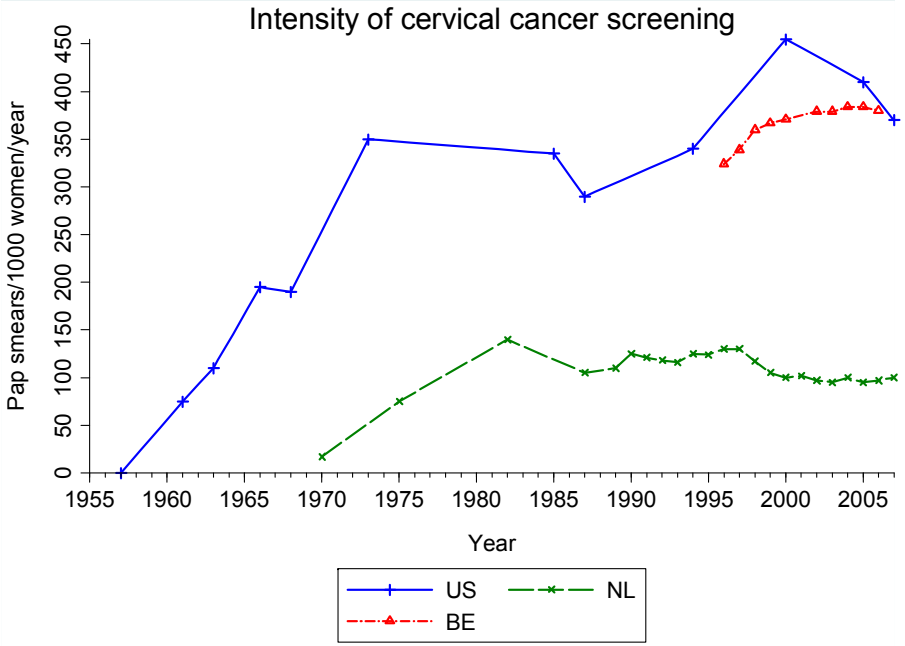
Period	Mean female population (25-64 years)	Number of smears taken[e]	Number of women screened <3years ago	3-year coverage	#smears/#women ratio
2002-2004	2 755 113	3 140 748	1 671 840	60.7%	1.14
2004-2006	2 785 516	3 199 984	1 706 043	61.2%	1.15

Table 54 – Consumption of Pap smears, five-year screening coverage and excess use between 2002 and 2006 for women between 25 and 64 years old

Period	Mean female population (25-64 years)	Number of smears taken	Number of women screened <5years ago	5-year coverage	#smears/ #women ratio
2002-2006	2 770 785	5 356 607	1 974 606	71.3%	1.93

[e] Only smears taken in the age group 25-64 years were considered.

Figure 51 – Intensity of cervical cancer screening in the US and the Netherlands, expressed as the standardized prevalence of an annual Pap smear per 1,000 women women/year (using the 2000 female population in the US as reference)[141] and the annual number of Pap smears in Belgium per 1000 women aged 25-64 years, in the period 1996-2006[4, 53]



8 COST IMPLICATIONS

8.1 Justification of the modelling approach

Many models for HPV screening are developed and are natural history models. In these class of models, a hypothetical cohort of women move in annual cycles through different health states, including HPV-infection and various pre-cancer and cancer states throughout their lifetime. Transitions from one state to another are defined by annual transition probabilities derived from the literature and sometimes calibrated to observed data, either from an RCT or from registry data. Those natural history models rely heavily on unobserved parameters such as progression and regression rates of CIN2 and CIN3; they are largely unobserved as for ethical reasons it is not possible to leave these lesions untreated. There is a growing interest in the concept of selecting calibrated parameter settings among modellers. However, attempts to estimate these parameters through calibration lead to a wide range of results whose epidemiological validity is difficult to assess or evaluate. Some models report a statistical measure of 'fit' to an independent dataset, but there is no commonly agreed way to interpret this fit or to judge if the fit is good or acceptable. Belgian data needed to parameterize or calibrate these models are not available and we would merely reproduce the already published findings of these models, as we would be obliged to use the same data.

Therefore we did not see an added value in adapting one of these natural history models and chose to model in a more direct way the results of the meta-analysis of RCT's measuring the relative effect of HPV screening compared to the effect of cytology screening on the incidence of CIN3 and cervical cancer.

8.2 Analytical choices for the cost implications

8.2.1 Model structure and (structural) assumptions

We constructed a time dependent state transition cohort model with annual cycles. We compared two cohorts:

- A cohort of 100 000 women undergoing screening every 3 years with cytology as entry test ('cytology screening' strategy).
- A cohort of 100 000 women undergoing screening every 5 years with HPV as entry test ('HPV screening' strategy).

Incidence and results of the screening tests were modelled separately, with a direct effect of HPV screening over cytology screening assumed, extrapolated from the RCT's. The following compartments were included in the model:

- Alive and susceptible to cervical cancer.
- Suffering from cervical cancer. This was modelled as a tunnel state of 5 additional compartments during which the women undergoes the excess mortality associated with cervical cancer. If the women survives she goes back to the susceptible state.
- Every 3 or 5 years a women can become screen positive. Additional compartments were then added for the confirmation test performed in series, depending on the result of the previous test. Additional compartments are also added for follow up tests of screen positive women.

Section 8.3 explains how the transition equations were calculated. Figure 52 shows the main structure of the model. The detailed algorithms for cytology and HPV screening are shown separately in Figure 53 and Figure 54, respectively.

Figure 52 – Main structure of the model

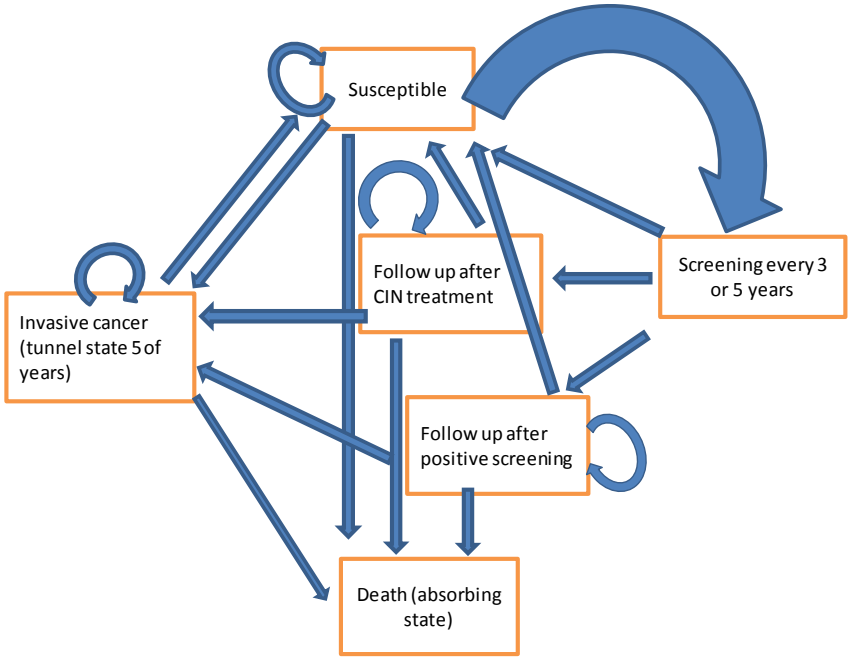


Figure 53 – Model structure: algorithm for cytology screening

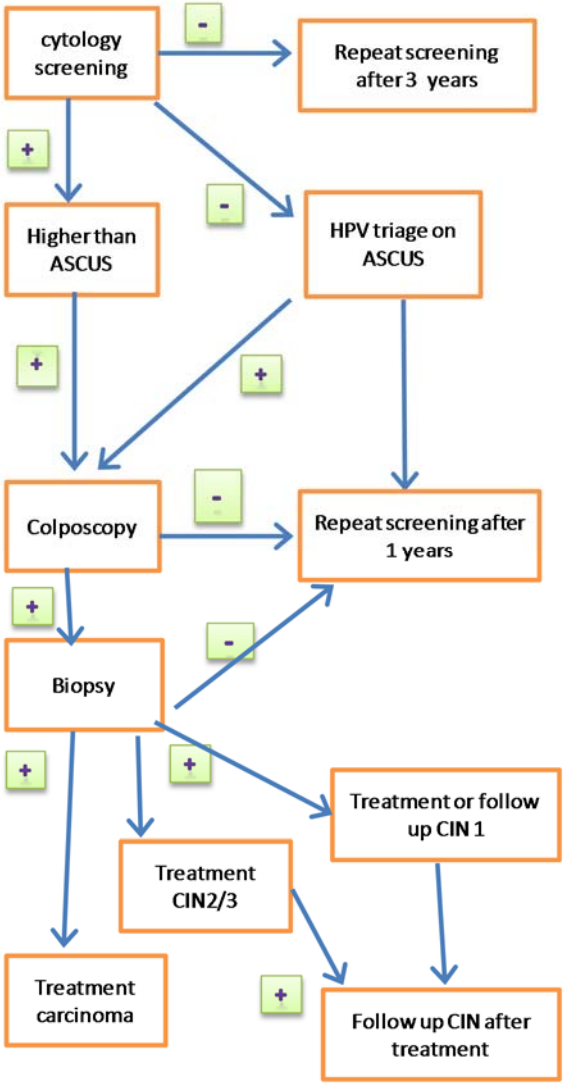
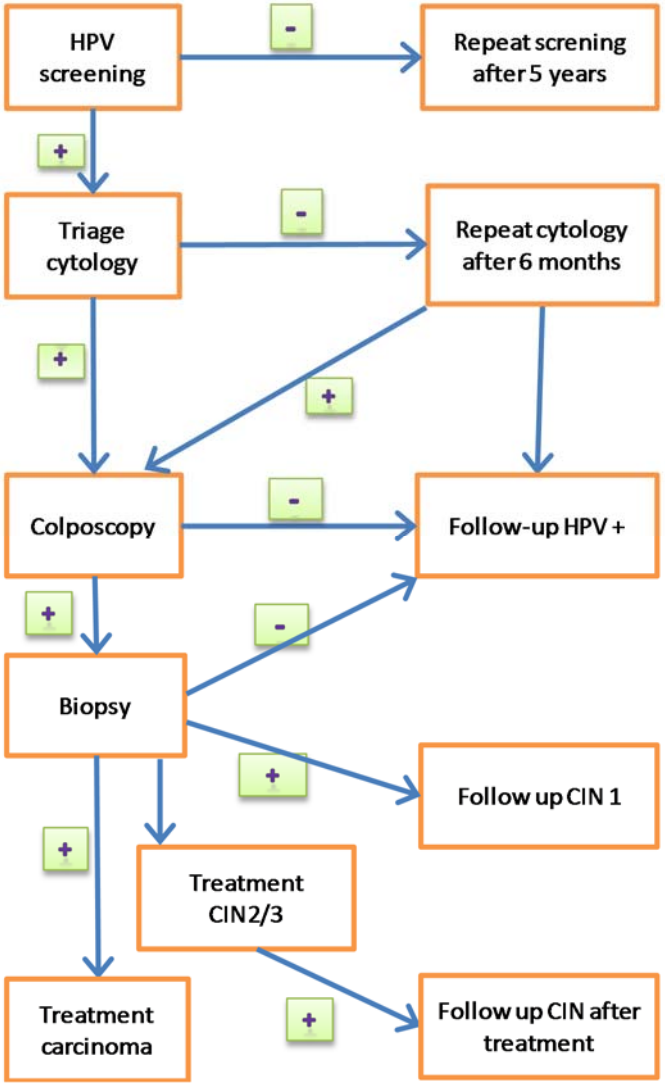


Figure 54 – Model structure: algorithm for HPV screening



8.2.2 Outcomes and comparator

The main outcomes of the model were cervical cancer cases and deaths averted, life year (LY) gained and cost-effectiveness. Main outcome for the cost-effectiveness analysis is the incremental cost per LY gained. In case of dominance, that is if a strategy costs less and prevents more LY than another strategy, incremental cost-effectiveness ratios (ICER) were not computed and the net savings and LY gained were reported separately.

8.2.3 Perspective

The economic evaluation was undertaken from the perspective of the health care payer, as recommended by the KCE guidelines[156]. Costs included were direct medical costs paid out of the health care budget (be it the federal government or the three federated entities) and the patients' out-of-pocket expenses for health care. Societal costs such as productivity losses and direct non-health care costs such as personal travel expenses were not accounted for.

All costs are expressed in Euro 2014. Costs from previous years were updated to 2014 using the health consumer price indices if needed[157].

8.2.4 Time horizon and discounting

The base-case time horizon of the model is 74 years: women enter the model at age 30 years and the cohort ends at 104 years, where all women were assumed to have died.

Future costs and benefits were discounted back to their present value. In the base-case a discount rate of 3% was applied to costs and 1.5% was applied to benefits, as recommended by the Belgian guidelines on economic evaluations[156].

8.3 Clinical and epidemiological parameters

8.3.1 Demographics

Population figures, natural death probabilities and life expectancies expressed by single year of age were taken from the most recent 2012 estimates for Belgium, published by the Belgian statistical authority "Statistical Belgium"[158].

8.3.2 Primary HPV screening

The data provided by RIATOL on the results of their test systematically applied to all samples in primary screening (see chapter 6) are the best estimates of the number of HPV positives we can expect. We applied the test positivity rates from Table 38 reported for age groups of 5 years.

We assume that all HPV positive women are retested with HPV after one year, and after two years if they are still positive after one year and after 3 years if they are still positive after 2 years. To estimate the transitions we use the proportion that become negative after a year as reported in the POBASCAM study by Bulkmans et al[77].

For cytological triage, we used the rate of 53% ASCUS+ after positive hrHPV test reported in the RIATOL data to estimate the number of women undergoing colposcopy. We further assumed that 50% of the women undergoing a colposcopy will also undergo a biopsy.

8.3.3 Primary cytology screening

We took the BCR/IMA data on cytological test results (Table 102) to estimate the proportion of screened women with a test result of higher grade than ASCUS; and that will need a colposcopy. In the sensitivity analysis we applied the age specific proportions reported by RIATOL.

We assumed that all cytology positive women are retested after one year and two years.

8.3.4 ASCUS that undergo re-reading and HPV as triage test

In Belgium ASCUS positive women must undergo an HPV triage test after re-reading of the ASCUS by a second person. We took the proportion (4%) of ASCUS positive women as reported in the BCR/IMA data as a parameter to estimate how many re-reading are needed. We assume that 60% of re-reading are positive, based on BCR/IMA data, and will need to be tested with a HPV triage test. Of those, we estimated the number of positive HPV tests to be 38%, based on the BCR/IMA data. In the sensitivity analysis we put this proportion to 60% (high scenario), this figure being the proportion of ASCUS + seen in the RIATOL data.

8.3.5 CIN1, CIN2 and CIN3

It is expected that HPV screening causes over-diagnosis of CIN lesions. For CIN1 it is not clear what effect can be expected. On the one hand HPV screening is more sensitive than cytology screening, but the increased screening interval (to 5 years) also leads to more CIN1 regressing. In 2012, Arbyn et al[6] reviewed the effect on CIN2 and CIN3 in RCTs. They found that the POBASCAM trial did not observe a difference between study arms in the detection of CIN2+ and CIN3+ over the first two rounds, but observed an excess of CIN2 in the HPV arm (ratio HPV vs. cytology group 1.33; 95% CI: 1.06–1.68). HPV testing was also used, however, in controls at the second round, allowing a more unbiased estimation of over-diagnosis. Several other European randomized controlled trials applied cytology at the second round. The SWEDESCREEN trial found no difference concerning CIN3+ (ratio HPV vs. cytology group 1.04, p = 0.20) but some excess of CIN2 in the HPV arm (ratio 1.56, p = 0.04). In ARTISTIC, the ratio was 1.18 (95% CI: 0.90–1.55) for CIN2 and 0.85 (95% CI: 0.67–1.08) for CIN3+. The NTCC trial found larger increases in the HPV group. Among women aged 35–60 years at recruitment, the HPV vs. cytology ratio was 1.65 (95% CI: 1.21–2.26) for CIN3 and 1.68 (95% CI: 1.25–2.26) for CIN2. The increase was larger among younger women (age 25–34 years at recruitment).

In order to estimate the number of CIN lesions, we used the data from the Belgian cancer register reported in Table 114 where the proportions of CIN lesions are reported for first screenings. However, these data only give a rather indirect estimation, as these are not the proportion of CIN in a screening done every 3 years or every 5 years with HPV, but a mixture of different time intervals. We assumed that by extending the screening interval the number per screening round would increase proportionally. This is a conservative assumption as you would expect more lesions to regress as time interval increases.

Therefore we take as baseline estimate for CIN 1 the proportion of CIN 1 reported by the BCR for the cytology cohort with no increase in the HPV cohort. In the sensitivity analysis we assume a possible increase of 10% and 65%. For CIN2, we take as baseline estimate the proportion of CIN2 reported by the BCR for the cytology cohort with a 30% increase in the HPV cohort. In the sensitivity analysis we assume a possible increase of 10% and 65%. For CIN3, we take as baseline estimate the proportion of CIN3 reported by the BCR for the cytology cohort with no increase in the HPV cohort. In the sensitivity analysis we assume a possible increase of 20% and a decrease of 15% in the HPV cohort, applying the increase and decrease reported in the RCT's.

8.3.6 Incidence of cervical cancer

We used the age specific (5-year age band) incidence rates from Belgium, as reported by the BCR, that are comparable across the three federated entities in Belgium. We took the average incidence calculated over the years 2004-2011. As these rates are derived among a mix of screened and unscreened women, they cannot be used directly in the screened cohorts. Therefore we made a proportional adjustment to estimate the incidence in the cohort screened with the current policy assuming a 60% 3 year participation rate (range 40 to 80%) to the current screening, as estimated in the IMA data. Due to the large variety in screening compliance and frequency in Belgium, this figure should rather be considered as an assumption. The European guidelines for quality control of cervical screening discusses the possible effect of opportunistic screening on cervical cancer incidence but estimates vary widely. We assumed a 50% effect of the current screening on incidence of cervix cancer. Therefore uncertainty around this figure is very important.

8.3.7 Effect of HPV screening on the incidence of cervical cancer

We used the result reported in section 1.2, based on the individual based meta-analysis of Ronco et al[154] and applied it directly to the assumed incidence as described above. In the base case analysis we assumed a reduction with a relative risk of 0.45. Although this is a direct measure,

primary studies have a follow up that does not exceed 8 years. We assumed that this rate ratio can be applied proportionally, although this is not sure, as the rate ratio increases with time in the meta-analysis. Therefore we take as high value 0.3, the rate ratio reported in women that were initially HPV negative, and a rate ratio of 0.8 as pessimistic lower limit. An even worse rate ratio of 1 was also tested in the sensitivity analysis.

As reported by Ronco et al[154], there is no indication that switching from cytology to HPV screening causes a stage shift in the invasive cancers. Therefore we assumed that the beneficial effect of HPV screening is only due to a reduction in incidence of invasive cervical cancer and not to a stage shift.

8.3.8 *Excess mortality due to cervical cancer*

We took the relative survival curves expressed annually over 5 years as reported by the Belgian Cancer Registry for the years 2004-2008. After 5 years we assumed that affected women experienced a survival similar to that of the general population. The Belgian cancer registry reports different survival rates for the age groups 15 to 44 and 45 to 64 years. We did not stratify the survival rates per stage, as there are no indications that there is a stage shift. Further breaking the data up comes at a price, as invasive cervical cancer is not so frequent numbers would become small and unstable. Relative survival at 1, 3 and 5 years were obtained directly from the data. Survival at 2 and 4 years was estimated by linear interpolation, which is a good approximation given the general form of the curve (see Table 55).

Table 55 – Relative survival to cervical cancer

Age group	Relative survival (%)				
	1 year	2 year	3 year	4 year	5 year
Data from the BCR					
15-44 years	96.9	-	88.3	-	85.7
45-64 years	90.3	-	75.9	-	70.1
Interpolated data					
15-44 years	96.9	92.6	88.3	87.0	85.7
45-64 years	90.3	83.1	75.9	73.0	70.1

8.4 Economic parameters

8.4.1 *Cytology*

The total cost of performing a cytology (€50.35), either as first screening test (and first reading) or as follow-up test, consists of the cost of one consultation to the general practitioner (GP) or the gynecologist (€23.06), the cost of sampling the smear (€4.99), and the cost of analysing the cytological smear (€22.30). This is in line with a previous study reporting comparable results[159].

The total cost for the second reading of a cytological smear is valued at €11.13.

These costs were estimated from the Belgian reimbursement scheme (the "nomenclature"), which contains the unit costs (including the patients share) of all health care services reimbursed by the Belgian health care insurance[160]. An overview of the costs is presented in Table 65.

Consultations

Taking into account the proportion of accredited versus non accredited professionals[161], the costs of 1 consultation to the GP and to the gynecologist are presented in the table below[160]. Based on the analyses of the IMA and CHP data, it was estimated that 10% of the smears would be taken by a GP and 90% by a gynaecologist. This results in an average cost of consultation of €23.06 (10% * €23.37 + 90% * €23.03).

Table 56 – Cost of a consultation to a GP and to a gynecologist

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
General practitioner			
101032	Consultation au cabinet par un médecin généraliste	Raadpleging in de spreekkamer door een huisarts	€20.92
101076	Consultation au cabinet par un médecin généraliste accrédité	Raadpleging in de spreekkamer door een geaccrediteerde huisarts	€24.48
Proportion of accredited general practitioner			68.69%
Average cost of a GP consultation			**€23.37**
Gynecologist			
102012	Consultation au cabinet par un médecin spécialiste autre que ceux cités aux nos 102034, 102174, 102196, 102211, 102071, 102093, 102115, 102130, 102152 et 102734	Raadpleging in de spreekkamer door een ander geneesheer-specialist dan die, vermeld onder de nrs. 102034, 102174, 102196, 102211, 102071, 102093, 102115, 102130, 102152 en 102734	€20.58
102535	Consultation au cabinet par un médecin spécialiste accrédité autre que ceux cités aux nos 102550, 102675, 102690, 102712, 102572, 102594, 102616, 102631, 102653 et 102756	Raadpleging in de spreekkamer door een ander geaccrediteerde geneesheer-specialist dan die, vermeld onder de nrs. 102550, 102675, 102690, 102712, 102572, 102594, 102616, 102631, 102653 en 102756	€24.48
Proportion of accredited specialists			62.75%
Average cost of a consultation to the gynecologist			**€23.03**

GP: general practitioner

Smear sampling

The cost of sampling a smear is valued at €4.99, whether the smear is taken from patients who are screened or are in follow-up, and whether the smear is sampled by a GP or a specialist (Table 57).

Table 57 – Cost of cytological smear sampling

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
114030 - 114041	Réalisation d'un frottis cervical et vaginal en vue d'un examen cytopathologique, effectué dans le cadre du dépistage de cellules néoplasiques	Nemen van een cervicaal en vaginaal uitstrijkpreparaat met het oog op een cytopathologisch onderzoek, uitgevoerd voor het opsporen van neoplastische cellen	€4.99
114170 - 114181	Réalisation d'un frottis cervical et vaginal en vue d'un examen cytopathologique, effectué dans le cadre d'un suivi diagnostic ou thérapeutique	Nemen van een cervicaal en vaginaal uitstrijkpreparaat met het oog op een cytopathologisch onderzoek, uitgevoerd voor een diagnostische of therapeutische follow-up	€4.99
149612 - 149623	Réalisation d'un frottis cervical et vaginal en vue d'un examen cytopathologique, effectué par un médecin spécialiste, dans le cadre du dépistage de cellules néoplasiques	Nemen van een cervicaal en vaginaal uitstrijkpreparaat met het oog op een cytopathologisch onderzoek uitgevoerd door een geneesheer-specialist voor het opsporen van neoplastische cellen	€4.99
149634 - 149645	Réalisation d'un frottis cervical et vaginal en vue d'un examen cytopathologique, effectué par un médecin spécialiste, dans le cadre d'un suivi diagnostic ou thérapeutique	Nemen van een cervicaal en vaginaal uitstrijkpreparaat met het oog op een cytopathologisch onderzoek uitgevoerd door een geneesheer-specialist voor een diagnostische of therapeutische follow-up	€4.99

Analysis

The cost of analysing the cytological smear is valued at €22.30 for a first reading of the screening test of for a follow-up test. The cost of performing a second reading of the cytological smear is valued at €11.13 (Table 58).

Table 58 – Cost of cytological smear analysis

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
First reading of screening test or follow-up test			
588350 - 588361	Honoraires pour la recherche lors d'un examen cyto-pathologique de dépistage de cellules néoplasiques sur prélèvement cervico-vaginal, quel que soit le nombre de prélèvements différents effectués et le nombre de frottis examinés	Honorarium voor het preventief cytopathologisch onderzoek voor het opsporen van neoplastische cellen op cervicovaginale afnamen, ongeacht het aantal uitstrijkpreparaten en ongeacht het aantal verschillende cervicovaginale afnamen	€22.30
588895 - 588906	Honoraires pour l'examen cyto-pathologique de dépistage de cellules néoplasiques sur prélèvement cervico-vaginal, dans le cadre d'un suivi diagnostic ou thérapeutique quel que soit le nombre de prélèvements différents effectués et le nombre de frottis examinés	Honorarium voor het cytopathologisch onderzoek voor het opsporen van neoplastische cellen op cervicovaginale afnamen, in het raam van diagnostische of therapeutische opvolging, ongeacht het aantal uitstrijkpreparaten en ongeacht het aantal verschillende cervicovaginale afnamen	€22.30
Second reading of screening test			
588873 - 588884	Honoraires pour l'examen complémentaire de deuxième lecture du frottis examiné en première lecture 588350 - 588361 pour la recherche lors d'un examen cyto-pathologique de dépistage de cellules néoplasiques sur prélèvement cervico-vaginal, quel que soit le nombre de prélèvements différents effectués et le nombre de frottis examinés	Honorarium voor het bijkomende cytopathologisch onderzoek voor het opsporen van neoplastische cellen op cervicovaginale afnamen, in tweede lezing naar aanleiding van de prestatie 588350 - 588361, op dezelfde cervico-vaginale afnamen, ongeacht het aantal uitstrijkpreparaten en ongeacht het aantal verschillende cervicovaginale afnamen	€11.13

8.4.2 HPV DNA

8.4.2.1 HPV DNA test as primary screening

As the HPV test in primary screening is not reimbursed for the moment we had to make an assumption about its potential cost. In the base case analysis the cost of €35 was used, in line with most published cost-effectiveness studies. The cost of an HPV test on a follow-up smear is currently set at €58.29 (Table 59). However, this cost is not in line with internationally accepted prices if the test could be used in primary screening. In the sensitivity analysis, the cost of an HPV test in primary screening was varied from €20 to €58.29.

8.4.2.2 HPV DNA test as triage or follow-up

The cost of performing an HPV DNA test as triage or follow-up on the same smear taken for cytology is valued at €58.29. If a new smear needs to be taken, the costs of one consultation to the GP/specialist (€23.06) during which the HPV smear is sampled (€4.99) are added. These costs were estimated from the Belgian reimbursement scheme (the "nomenclature")[160].

Consultation

If required, it was estimated that 10% of the HPV smears would be sampled by a GP and 90% by a gynecologist, which resulted in an average cost of consultation of €23.06 (10% * €23.37 + 90% * €23.03), see Table 56.

Smear sampling

The cost of sampling a smear for an HPV test was assumed to be equal to the cost of sampling smear for a cytology, i.e. €4.99 (Table 57).

Analysis

The cost of performing an HPV test is valued at €58.29, as reported in Table 59 below.

Table 59 – Cost of HPV DNA testing

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
588932 - 588943	Honoraires pour la recherche de l'HPV à haut risque au moyen d'une méthode de diagnostic moléculaire sur le même prélèvement cervico-vaginal que la prestation 588350 - 588361 ou 588873 – 588884	Honorarium voor het opsporen van hoogrisico HPV op cervicovaginale afnamen, door middel van een moleculair-diagnostische methode naar aanleiding van de prestatie 588350 - 588361 of 588873 - 588884, op dezelfde cervico-vaginale afname(n)	€58.29
588954 - 588965	Honoraires pour la recherche d'HPV à haut risque sur des prélèvements cervico-vaginaux au moyen d'une méthode de diagnostic moléculaire dans le cadre d'un suivi diagnostique ou thérapeutique, sur le même prélèvement cervico-vaginal que la prestation 588895 – 588906	Honorarium voor het opsporen van hoogrisico HPV op cervicovaginale afnamen, door middel van een moleculair-diagnostische methode in het raam van diagnostische of therapeutische opvolging, naar aanleiding van de prestatie 588895 - 588906, op dezelfde cervico-vaginale afname(n)	€58.29

8.4.3 Colposcopy

The total cost of performing a colposcopy (€36.49) on screened positive women consists of the cost of one consultation to the gynaecologist (€23.03) plus the cost of the colposcopy itself (€13.46). These costs were estimated from the Belgian reimbursement scheme (the "nomenclature") (Table 60)[160].

Consultation

It was estimated that all colposcopies would be performed by a gynaecologist, which resulted in an average cost of consultation of €23.03 (Table 56).

Colposcopy

The cost of the colposcopy is valued at €13.46, as reported in the table below (Table 60).

Table 60 – Cost of colposcopy

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
431955-431966	Colposcopie microscopique	Microscopische colposcopie	€13.46

8.4.4 Biopsy

The total cost of performing a biopsy was estimated at €71.59. This cost covers the sampling of the biopsy (€8.08) and its analysis (€63.51) by an anatomo-pathologist. These costs were estimated from the Belgian reimbursement scheme (the "nomenclature").[160] Note further that those costs are in line with a previous study reporting comparable results (Table 61)[159].

Consultation

We assumed that if lesions are identified by the colposcopy, the biopsy would be performed at the same time, during the consultation planned for colposcopy. We therefore attributed no additional cost of consultation for the biopsy itself.

Biopsy sampling

The cost of biopsy sampling is valued at €8.08 according to the Belgian reimbursement scheme.

Table 61 – Cost of biopsy sampling

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
432110 - 432121	Prélèvement par pince d'un fragment du col et/ou électrocoagulation	Afname met tang van een fragment van de hals en/of elektrocoagulatie	€8.08

Biopsy analysis

Examination of the biopsy by an anatomo-pathologist is valued at €63.51, as reported in Table 62.

Table 62 – Cost of biopsy examination

Code	Nomenclature label (French)	Nomenclature label (Dutch)	Cost (2014)
588011 - 588022	Honoraires pour l'examen anatomo-pathologique par inclusion et coupe d'autant de prélèvements que nécessaire, quel que soit le nombre de coupes et quel que soit le nombre d'organes examinés, y compris l'examen macroscopique éventuel des pièces opératoires, pour les prélèvements ne correspondant pas aux prestations 588232 - 588243, 588254 - 588265, 588276 - 588280 ou 588291 - 588302	Honorarium voor het pathologisch-anatomische onderzoek door inclusie en coupe van zoveel prelevementen als nodig, ongeacht het aantal coupes en ongeacht het aantal onderzochte organen en met inbegrip van het eventueel macroscopisch onderzoek van operatiestukken, voor die prelevementen die niet overeenkomen met de prestaties 588232 - 588243, 588254 - 588265, 588276 - 588280 of 588291 - 588302	€63.51

8.4.5 Cervical intra-epithelial neoplasia

The direct medical costs of treating the cervical intra-epithelial neoplasia (CIN) of different stadia were derived from a recent Belgian economic burden study.[162] Hospital-related and outpatient management costs associated with CIN were derived from a retrospective analysis of the IMS Hospital Disease Database (2004) and from the description of typical treatment pathways for CIN by clinical experts. Hospital costs of conisations and hysterectomy were identified from the IMS database by selecting records with ICD-9 codes 67.2 (conisation of cervix) and 68.3-68.9 (hysterectomies) as primary diagnosis. Ambulatory resources (e.g. conisation, laser therapy, cryotherapy, consultations...) consumed for the management of CIN were described by the experts and were valued based on the Belgian reimbursement scheme[160]. The costs of CIN treatments (including the RIZIV-INAMI and the patient costs) are reported in Table 63.

Table 63 – Direct medical costs of CIN

Health state	Treatment costs	
	Reported in the study[162] (Eur 2006)	Converted in Eur 2014 values
CIN1	€251.80	€294.43
CIN2	€331.50	€387.62
CIN3	€414.50	€484.67

CIN: cervical intra-epithelial neoplasia.

In a previous study, the direct medical costs of treating CIN2/3 were estimated at €431, which is line with the above figures. In this study treatment consisted of a conisation, a one-day hospitalisation, a consultation to the gynaecologist, the honorarium for the aenesthesiologist and the honorarium for the post-op analysis of the resected tissues[159].

8.4.6 Cervical cancer

The total direct medical costs associated with patients hospitalised for cervical cancer were also derived from the recent study of Annemans et al[162]. The IMS Hospital Disease Database was analysed for the year 2004. Records were selected based on ICD-9-CM diagnostic code 180 (i.e. malignant neoplasm of cervix uteri) as principal diagnosis to determine the direct medical costs of a hospital stay for cervical cancer. These costs are presented in Table 64.

Table 64 – Hospitalisation costs for cervical cancer

Cervical cancer stage	Number (%) of hospital stays due to cervical cancer (IMS database, 2004)	Treatment costs	
		Reported in the study[162] (Eur 2006)	Converted in Eur 2014 values
FIGO I	112 (64%)	€6777	€7924
FIGO II + III	22 (13%)	€8495	€9933
FIGO IV	41 (23%)	€18 400	€21 515
Total	175 (100%)	€9716	€11 361

FIGO: International federation of gynaecology and obstetrics; IMS: Intercontinental Marketing Services.

8.4.7 Summary

Table 65 presents an overview of the cost input parameters used in the simulation model.

Table 65 – Cost input parameters (Eur 2014, health care payer perspective)

Parameters	Cost (Eur 2014)	Source
Cytology – First reading screening tests and follow-up test	€50.35	Belgian nomenclature
Cytology – Second reading screening test	€11.13	Belgian nomenclature
HPV DNA – Primary screening	€35	Assumption
HPV DNA – Triage and follow-up	€58.29	Belgian nomenclature
Colposcopy	€36.49	Belgian nomenclature
Biopsy	€71.59	Belgian nomenclature
Cervical intra-epithelial neoplasia (CIN)		
CIN 1	€294.43	Annemans, 2008
CIN2	€387.62	Annemans, 2008
CIN3	€484.67	Annemans, 2008
Cervical cancer		
FIGO I	€7924	Annemans, 2008
FIGO II + III	€9933	Annemans, 2008
FIGO IV	€21 515	Annemans, 2008
Overall	€11 361	Annemans, 2008

FIGO: International federation of gynaecology and obstetrics. Sources: Belgian nomenclature[160] and Annemans, 2008[162].

8.5 Uncertainty

Uncertainty around the model parameters was explored by running the model under a number of different scenarios (univariate and multivariate). In the univariate scenario analyses, the base case model was run by considering higher and/or lower values for a large range of uncertain clinical, epidemiological and screening parameters, separately. The cost of the HPV test used as primary screening, for which an assumption had to be made, was also varied in univariate scenario analyses. A multivariate scenario analysis, against HPV screening, was also performed by simultaneously varying several clinical parameters to their worst estimate. Table 66 lists the scenario analyses performed on the base case model. A probabilistic sensitivity analysis was not performed because the data collected did not allow to inform a meaningful probability distribution for most of the parameters in the model.

Table 66 – Parameters varied in the univariate scenario analyses

Parameter	Base case	Low scenario	High scenario
Values cytology screening			
Proportion ASCUS +	0.04	0.02	0.06
Proportion ASCUS + after re-reading	0.60	0.40	0.80
HPV+ among ASCUS + tested for triage	0.38	0.20	0.60
Proportion higher grade than ASCUS	0.03	0.02	0.06
Proportion CIN1 per screening round	0.004982	0.002	0.006
Proportion CIN2 per screening round	0.002788	0.001	0.006
Proportion CIN3 per screening round	0.002748	0.001	0.006
Proportion of women undergoing colposcopy where a biopsy is taken	0.50	0.20	0.80
Values HPV screening			
Proportion cytolgy triage + after HPV +	0.53	0.40	0.60
Proportion of women undergoing colposcopy where a biopsy is taken	0.50	0.20	0.80
Proportion CIN1 per screening round	0.008303	0.0058	0.0125
Proportion CIN2 per screening round	0.006040	0.0046	0.0084
Proportion CIN3 per screening round	0.004580	0.0039	0.0055
Effect HPV on cervical cancer incidence	0.45	0.30	0.80
Proportion hr-HPV persisting after one year	0.50	0.30	0.70
Cost of HPV test used in primary screening	€35	€20	€58.29
Common to two cohorts			
Effectiveness current screening (relative risk screened vs. unscreened)	0.50	0.40	0.60
Coverage rate of the cervical cancer screening	0.60	0.40	0.80

8.6 Results

8.6.1 Base case

Table 67 shows the results of the base case analysis. If women undergo cervical cancer screening every 3 year with cytology as entry test ('cytology screening' strategy), the model predicts that 462 cervical cancer cases, resulting in 178 deaths, would occur over the lifetime of a cohort of 100 000 women, with the cost of screening and treatment totalling €83 million.

If cytological primary screening is replaced by HPV primary screening, 240 cervical cancer cases and 95 deaths (or 2878 life years) could be prevented. HPV screening would further result in net savings (- €14 million), mainly due to the extension of the screening interval from 3 to 5 years. The base case analysis shows thus that HPV screening dominates cytology screening as it costs less and avoids more cervical cancer cases/deaths than cytology screening.

Table 67 – Results from the base case analysis (per cohort of 100 000 women)

Outcome	Cytology screening	HPV screening	Incremental outcomes
Cervical cancer cases	462	222	-240
Cervical cancer deaths	178	82	-95
Life years	5 337 361	5 340 240	2878
Life years (discounted)	3 658 751	3 660 369	1618
Total costs	€83 066 833	€68 179 074	- €14 887 760
Total costs (discounted)	€51 786 706	€46 004 382	- €5 782 324

Incremental outcomes are values for HPV screening minus values for cytology screening. For discounted values, a discount rate of 3% was applied to costs and 1.5% was applied to benefits, as recommended by the Belgian guidelines on economic evaluations.

8.6.2 Scenario analyses

As shown Table 68, switching to HPV screening remained both less costly and more clinically effective (i.e. HPV screening is dominant) under near all univariate scenario analyses explored. Incremental cost-effectiveness ratios (ICER's) were only computed for a limited number of scenarios. Detailed results of the scenario analyses can be found in appendix.

Results were most sensitive to the likely effect of the HPV test on the incidence of invasive cervical cancer and the cost of HPV testing. Increasing the effect of HPV on the incidence cervical cancer to 0.8 (instead of 0.45) resulted in a 64% decrease in the number of LY saved (from 2878 to 1047 LY gained), but HPV screening remained dominant. Even assuming that HPV has no additional beneficial effect over cytology (rate ratio of 1), the HPV strategy remained a dominant option. HPV screening was no longer dominant when the price of the HPV test was set at €58.29 (i.e. the current price of the HPV test as a follow-up test), instead of €35 in the base case. However, the cost per LY gained of this scenario remained low at €4319.

Varying the baseline incidence of cervical cancer, by modifying the assumptions on the coverage rate and the effectiveness of cytology screening as explained in 8.3.6, had an important effect on the number of life years saved but only a modest effect on cost, such that HPV screening remained dominant. For example, increasing the participation to cytology screening to 80% (instead of 60% in the base) decreases the incidence of cervical cancer and reduces the number of LY saved by HPV screening by 20% (from 2878 to 2312 LY gained). Though slightly reduced, HPV screening still results in net savings (€14.4 million instead of €14.8 in the base case), such that HPV screening remains a dominant option.

In a multivariate scenario analysis penalizing HPV screening, in which it was assumed that 1) HPV screening had no additional beneficial effect on invasive cervical cancer, 2) the incidence of CIN1, CIN2 and CIN3 are increased by 50%, 80% and 20%, respectively, 3) the number of false positives with HPV screening is increased by with 47% and 4) the number of false positives with cytology screening is reduced by 50% (i.e. cytology screening is much more specific), HPV screening still leads to net savings (of about €114 832 per cohort) with an equivalent number of life years saved compared to cytology screening.

Table 68 – Results from the scenario analyses (per cohort of 100 000 women), HPV screening versus cytology screening

Scenario description			Cervical cancer cases averted	Cervical cancer deaths averted	Life year gained	Net costs[a]	ICER: cost per LY gained
Base case results	-	-	*240*	*95*	*2878*	*-€ 14 887 760*	*HPV dominant*
Cost parameters							
Cost of HPV test used in primary screening	Low	€20	240	95	2878	-€ 27 696 687	HPV dominant
	High	€58.29	240	95	2878	€ 5 000 235	€ 4 319
Cytology screening parameters							
Proportion ASCUS +	Low	0.02	240	95	2878	-€ 12 088 470	HPV dominant
	High	0.06	240	95	2878	-€ 17 687 050	HPV dominant
Proportion ASCUS + after re-reading	Low	0.40	240	95	2878	-€ 13 682 013	HPV dominant
	High	0.80	240	95	2878	-€ 16 093 507	HPV dominant
HPV + among ASCUS + tested for triage	Low	0.20	240	95	2878	-€ 14 080 512	HPV dominant
	High	0.60	240	95	2878	-€ 15 874 396	HPV dominant
Proportion higher grade than ASCUS	Low	0.20	240	95	2878	-€ 13 205 993	HPV dominant
	High	0.60	240	95	2878	-€ 20 680 511	HPV dominant
Proportion CIN1 per screening round	Low	0.002	240	95	2878	-€ 13 777 835	HPV dominant
	High	0.006	240	95	2878	-€ 15 266 722	HPV dominant
Proportion CIN2 per screening round	Low	0.001	240	95	2878	-€ 14 561 296	HPV dominant
	High	0.006	240	95	2878	-€ 16 155 112	HPV dominant
Proportion CIN3 per screening round	Low	0.001	240	95	2878	-€ 13 983 638	HPV dominant
	High	0.006	240	95	2878	-€ 16 569 886	HPV dominant
Proportion of women undergoing colposcopy where a biopsy is taken	Low	0.20	240	95	2878	-€ 13 961 345	HPV dominant
	High	0.80	240	95	2878	-€ 15 814 174	HPV dominant
HPV screening parameters							
Proportion cytology triage + after HPV +	Low	0.40	240	95	2878	-€ 15 034 435	HPV dominant
	High	0.60	240	95	2878	-€ 14 808 781	HPV dominant
Proportion of women undergoing colposcopy where a biopsy is taken	Low	0.20	240	95	2878	-€ 15 746 830	HPV dominant
	High	0.80	240	95	2878	-€ 14 028 690	HPV dominant
Proportion CIN1 per screening round	Low	0,0058	240	95	2878	-€ 15 458 483	HPV dominant
	High	0,0125	240	95	2878	-€ 13 936 554	HPV dominant
Proportion CIN2 per screening round	Low	0,0046	240	95	2878	-€ 14 768 069	HPV dominant
	High	0,0084	240	95	2878	-€ 15 087 244	HPV dominant

Proportion CIN3 per screening round	Low	0,0039	240	95	2878	-€ 14 828 772	HPV dominant
	High	0,0055	240	95	2878	-€ 14 966 410	HPV dominant
Effect of HPV on cervical cancer incidence (relative risk)	Low	0.30	305	120	3663	-€ 15 620 549	HPV dominant
	High	0.80	87	39	1047	-€ 13 177 918	HPV dominant
Proportion hr-HPV persisting after one year	Low	0.30	240	95	2878	-€ 15 963 499	HPV dominant
	High	0.70	240	95	2878	-€ 13 506 245	HPV dominant
Parameters common to both screening strategies (parameters determining the baseline incidence of cervical cancer)							
Effectiveness current screening (relative risk of screened versus unscreened)	Low	0.40	210	83	2519	-€ 14 542 414	HPV dominant
	High	0.60	280	111	3358	-€ 15 348 221	HPV dominant
Coverage rate of the cervical cancer screening	Low	0.35	305	121	3663	-€ 15 641 242	HPV dominant
	High	0.80	193	77	2312	-€ 14 344 264	HPV dominant

a. Net costs: total costs of HPV screening minus total costs of cytology screening.

8.7 Discussion

The model suggests that net savings could be achieved in Belgium by switching from cytological to HPV screening, and that this would be associated with an increase in the number of cervical cancer cases and deaths avoided and life-years saved. The sensitivity analysis showed that these conclusions hold under a broad range of plausible and even pessimistic assumptions.

There are concerns that the increased sensitivity of HPV comes at the cost of a lower specificity, a fact that in principle could lead to increased cost. In the Belgian context however this effect is less important for several reasons. First, both the data provided by Riatol and by the BCR-IMA show that the number of cytology positive women is already relatively high in Belgium, around 7%. A second element is the fact that colposcopy is relatively cheap in Belgium, compared to other countries.

The estimations on the impact on cost are more robust than the estimations on the effect. Although it has been shown in RCT's that HPV screening is more effective than cytology based screening it is not clear how these effects should be extrapolated beyond the duration of the primary studies, as the effect was increasing over the study period. This implies that the effect may well be more important in the long run.

Cohort studies, as reported in chapter 1.2.3.2 show that incidence of CIN3 and cervical cancer among HPV negative patients over a 5 year period is very low but that incidence in HPV positive/cytology negative patients is important. Therefore we foresaw a yearly follow up of HPV positive patients as long as they remain HPV positive. There is no consensus about this, but we opted for this conservative assumption.

The data of BCR-IMA show that for the moment cytology screening in Belgium is not applied in a way that is neither very consistent nor optimal, an example of this is the excessive use of colposcopy and the large variation in cytology results. We used an algorithm for cytology screening that we think is a good representation on how cytology screening should be done in an optimal way.

In general all models can be criticized in the sense that they are a simplification of the reality. This model is no exception. However we used parameters that could directly be observed instead of estimating unobserved parameters by calibration in a natural history model, for reasons that we explained in the introduction. This makes the model more transparent but we are still confronted with considerable structural uncertainty. We explored this structural uncertainty with an extensive sensitivity analysis.

As discussed in chapter 4 there are different triage algorithms possible. However, differences in cost and effects are small compared to the rest of the cost and given the large structural uncertainty very difficult to evaluate. Moreover, cytology triage before colposcopy is not only a matter of cost but also of acceptability and feasibility, and cost implications do not properly reflect this.

We used €35 as a base case estimation for an HPV test in routine and not the current Belgian reimbursed price for a follow up or triage HPV, as these are way above what is internationally used. A centrally negotiated price could lower the price even more.

Our finding that HPV screening is cost saving and more clinically effective is in line with other studies, done in neighboring countries such as the Netherlands, UK, Germany and Norway. We did not take into account the effect of HPV vaccination as HPV testing is not applied before the age of 30 years. It is possible that in the future this will be needed.

APPENDICES

APPENDIX 1. ANALYSIS OF IMA AND CHP DATA

Appendix 1.1. Role of HPV DNA tests in cervical cancer screening

Appendix 1.1.1. Introduction: available data

This study aims at contributing to better understand the role of HPV tests in cervical cancer screening. To do so, two databases available at Belgian Cancer Registry (BCR) were analysed.

IMA database

The IMA database contains the list of nomenclature codes of all reimbursed medical acts related to cervical cancer screening that have been performed in Belgium from the year 2008 to the first semester of 2013. The database contains the following information: Social Security Number (SSN) of patients, date of medical act, nomenclature codes of medical acts and codes identifying the laboratory where the samples were analyzed.

The nomenclature codes found in the IMA database correspond to the following medical acts:

- Sampling of cervix cytology:
  - Screening test by general practitioner (114030, 114041) or specialist (149612, 149623)
  - Follow-up test by general practitioner (114170, 114181) or specialist (149634, 149645)
- Microscopic colposcopy (431955, 431966)
- Further diagnosis and/or treatment (149052, 149063, 431270, 431281, 431314, 431325, 431336, 431340, 431351, 431362, 431491, 431502, 431911, 431922, 432110, 432121, 432154, 432165, 432294, 432305, 432670, 432681, 432736,432740, 220290, 220301, 244915, 244926, 244930, 244941, 431292, 431303, 432390, 432401, 432655, 432666)
- Analysis of cervix cytology:

  - First reading of a screening test (588350, 588361*) *the code 5885361 is erroneously not present in the IMA database. However, since this code corresponds to a first reading of a sample from a hospitalized patient, it should not represent many cases. For example, the number of cervix samplings on hospitalized patients (114041-149623) represented 0.27% of the total number of cervix samplings in 2011. A similar proportion is therefore expected for the first readings of samples from hospitalized patients.
  - Second reading of a screening test (588873, 588884)
  - Follow-up test (588895, 588906)
- Analysis of HPV
  - After abnormal screening test (588932, 588943)
  - As part of follow-up examination (588954, 588965)

There were two deliveries of these IMA data:

- Delivery of April 2013: medical acts performed in years 2008 – 2011
- Delivery of November 2013: medical acts performed in years 2011-2013 (most recent date 28/06/2013).

Both deliveries were merged into one IMA database. The database with medical claims data can be considered as complete for the years 2008, 2009 and 2010. Because of a delay between the date of the medical act and its registration, the medical claims database is incomplete for the years 2011, 2012 and 2013. Moreover, for 2013 we received the data only until June (28/06/2013).

Note: some nomenclature codes were introduced in 2009. In 2013 the reimbursement changed for certain codes. These modifications are described later in section 2.1.

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Cyto-histo pathology register (CHP)

The cyto-histo pathology register (CHP) contains the diagnosis/result of all analyses (reimbursed and not reimbursed) performed on cervix samples by anatomopathological laboratories in Belgium. The database contains information such as the SSN of patient, date of analysis, result/diagnosis of the analysis, laboratory, and nomenclature codes. Those data are delivered by laboratories to BCR before being treated by internal software. Currently, only a part of the data of year 2011 has been treated by BCR. In order to increase the exhaustivity of HPV tests in the CHP, a priority was given during data treatment to the laboratories performing HPV tests and encoding the HPV results. Of the 91 laboratories that delivered data of cervical samples, data of 62 laboratories were treated and are available in the CHP for this study.

Appendix 1.1.2. Analysis of IMA database 2008-first semester 2013

Appendix 1.1.2.1. Global overview of IMA database

Firstly, the IMA data were analyzed in order to have an overview of the number of reimbursed medical acts performed in Belgium between 2008 and the first semester of 2013. The first step in the analysis was a data cleaning step. As shown in Table 69, the IMA database contains 51 774 records that have the same SSN, the same date and the same nomenclature code. These duplicates were removed from the IMA database before performing further analyses.

Table 69 – Number of duplicate records (i.e. records with same SSN, date and nomenclature code) per year in the IMA database

2008	2009	2010	2011	2012	2013	Total
9 395	9 032	8 622	8 610	11 755	4 360	51 774

After the data cleaning step, the IMA database contains 12 660 639 records and 2 694 547 unique SSN (Table 70).

Table 70 – Number of records and unique SSN in the IMA database per year

	2008	2009	2010	2011	2012	2013	Total
Number of records	3 055 414	2 546 316	1 997 173	2 324 990	2 109 789	626 957	12 660 639
Number of unique SSN	1 315 825	1 154 905	950 758	1 069 408	988 165	352 602	2 694 547

The nomenclature codes available in the IMA database were divided into following categories:

- ***SCREENING***: Smear sampling and analysis of samples taken in the context of screening. This category is subdivided into 'sampling' or 'analysis' and 'sample type' (= cytology or HPV) (see Table 71).
- ***FOLLOW-UP***: Smears taken from patients who are in follow-up. This category is subdivided into 'sampling' or 'analysis' and 'sample type' (= cytology or HPV) (see Table 71)
- ***COLPOSCOPY***: See Table 72.
- ***FURTHER DIAGN/TREAT***: Nomenclature codes that correspond to further diagnosis after abnormal test results or treatment of cervical diseases (see Table 72).
- ***EXTRA***: Nomenclature codes that can correspond to further diagnosis after abnormal test results or treatment of cervical diseases, but not necessarily. Since these nomenclature codes are not always correlated to cervical abnormalities or cervical diseases, these codes are left out this analysis (see Table 72).

The nomenclature codes corresponding to each category and the number of reimbursed medical acts for the period 2008- 2013 are shown in Table 71 and Table 72.

Figure 55 below shows the theoretical time line between medical acts according to the KB/AR of 4/05/2009 and 11/02/2013. The nomenclature codes for medical acts which are done after the first reading of a screening test (second reading and HPV test) were introduced in 2009. At the same moment nomenclature codes for sampling, reading and HPV test in the context of follow-up were created. Consequently the analyses of these newly introduced medical acts are only reported from 2009 on. Also, the reimbursement of screening samples was allowed once each two years from 2009 on. Medical acts for sampling, reading and HPV test in the context of follow-up are reimbursed twice a year.

By the KB/AR of 11/02/2013, the reimbursement of medical acts in the context of screening was modified from once each two years to once each three years from 01/03/2013. Since the KB/AR of 14/01/2013, the use of colposcopy is no longer reimbursed if used as screening method from 01/02/2013.

Figure 55 – Theoretical time line of medical acts according to the KB/AR of 4/05/2009 and 11/02/2013

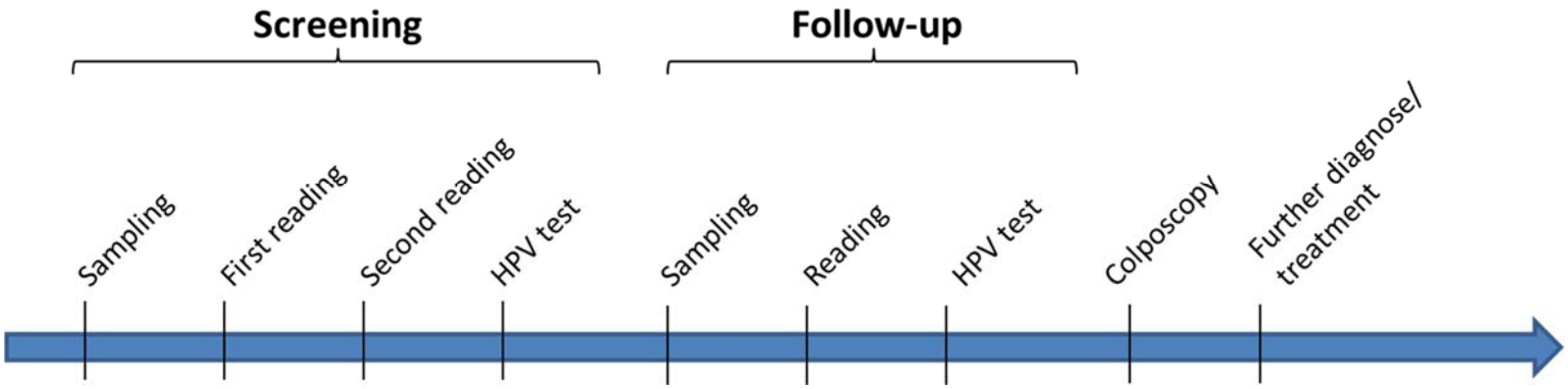


Table 71 – Number of reimbursed medical acts per nomenclature code for the categories 'SCREENING' and 'FOLLOW-UP' (period 2008- 2013)

Nomenclature	Category	Sampling/analysis	Sample type	Number of records
114030-114041 §	SCREENING	SAMPLING - GP	CYTO	432 104
149612-149623 §	SCREENING	SAMPLING - SP	CYTO	4 254 756
588350-588361 §	SCREENING	ANALYSIS - first reading	CYTO	4 931 165
588873-588884 *,§	SCREENING	ANALYSIS - second reading	CYTO	113 496
114170-114181 *,†	FOLLOW-UP	SAMPLING	CYTO	26 011
149634-149645 *,†	FOLLOW-UP	SAMPLING	CYTO	309 013
588895-588906 *,†	FOLLOW-UP	ANALYSIS	CYTO	335 009
588932-588943 *,§	SCREENING	ANALYSIS	HPV	79 950
588954-588965 *,†	FOLLOW-UP	ANALYSIS	HPV	84 953
			TOTAL	10 566 457

GP: General practitioner - SP: Specialist - Nomenclature codes introduced on 04/05/2009 - § Maximum 1 medical act per SSN/woman reimbursed each two year after reimbursement modifications in 2009 - Maximum 1 medical act per SSN/woman reimbursed each three year after reimbursement modifications in 2013 - † Maximum 2 medical acts per SSN/woman reimbursed per year after reimbursement modifications in 2009.*

Table 72 – Number of reimbursed medical acts per nomenclature code for the categories 'COLPOSCOPY', 'FURTHER DIAGN/TREAT' and 'EXTRA' (period 2008-2013)

Nomenclature	Category	Number of records
431955-431966 *	COLPOSCOPY	1 569 442
149052-149063	FURTHER DIAGN/TREAT	22 872
431270-431281	FURTHER DIAGN/TREAT	19 447
431314-431325	FURTHER DIAGN/TREAT	24 300
431336-431340	FURTHER DIAGN/TREAT	1 627
431351-431362	FURTHER DIAGN/TREAT	3 393
431491-431502	FURTHER DIAGN/TREAT	6 706
431911-431922	FURTHER DIAGN/TREAT	869
432110-432121	FURTHER DIAGN/TREAT	103 677
432154-432165	FURTHER DIAGN/TREAT	188
432294-432305	FURTHER DIAGN/TREAT	43 055
432670-432681	FURTHER DIAGN/TREAT	10 676
432736-432740	FURTHER DIAGN/TREAT	8 066
220290-220301	EXTRA	161 030
244915-244926	EXTRA	1 897
244930-244941	EXTRA	1 424
431292-431303	EXTRA	1 125
432390-432401	EXTRA	110 796
432655-432666	EXTRA	3 592
	TOTAL	2 094 182

** Since the KB/AR of 14/01/2013, the use of colposcopy is no longer reimbursed if used as a screening method from 01/02/2013 on.*

Appendix 1.1.2.2. Number of reimbursed medical acts per year

The tables below give the total number of IMA records per year (between 2008 and the first semester of 2013) for the following medical acts: a first reading of a screening test (Table 73), a second reading of a screening test (Table 74), a follow-up test (Table 75), a HPV test (Table 76), a colposcopy (Table 77), or a further diagnosis/treatment (Table 77).

Some medical acts can be reimbursed more than once a year for one patient. This means that a certain number of women are counted more than once a year. Therefore, the number of medical acts for each unique woman or SSN for each year is also counted. The corresponding numbers can be found in Tables 5 – 9 for the (gray) lines where the column 'unique SSN/ year' mentions 'yes'.

As shown in Table 73, 72 310 (5.7%) of the 1 264 346 screening samplings performed in 2008 were done on the same SSN/woman. This percentage decreases to 0.3% in 2010 and 2011 and to 0.25% in 2012.

Most of screening samplings and follow-up samplings were performed by specialists (90 to 94%) (see Table 73 & Table 75 and Figure 56 & Figure 57).

The proportion of HPV tests performed in the context of follow-up in relation to the total number of HPV tests has slightly increased from 47% in 2009 to 57.3% in 2013 (Table 75 and Figure 57).

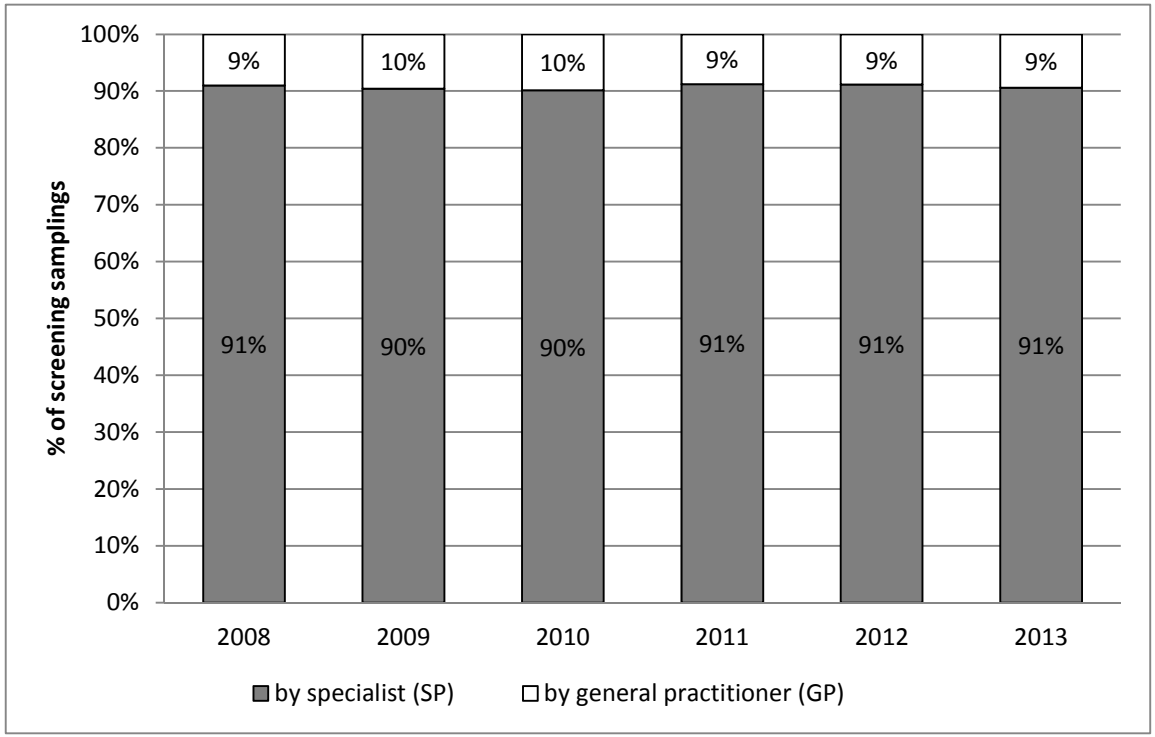
There is a significant decline in the total number of colposcopies (Table 77).

Table 73 – Number of first readings of screening tests per year (sampling and analysis)

	Nomenclature	Unique SSN/year (*)	Year (§)					
			2008	2009	2010	2011	2012	2013
Number of first readings of screening tests - sampling - global	114030-114041 149612-149623	no	1 264 346	995 983	673 983	816 284	717 169	219 095
Number of first readings of screening tests - sampling – by general practitioner	114030-114041	no	114 036	95 418	66 505	71 973	63 542	20 630
Number of first readings of screening tests - sampling - by specialist	149612-149623	no	1 150 310	900 565	607 478	744 311	653 627	198 465
Number of first reading of a screening test - analysis	588350-588361	no	1 329 910	1 022 976	712 950	875 098	766 912	223 319
Number of first readings of screening tests - per SSN - sampling - global	114030-114041 149612-149623	yes	1 192 036	971 315	671 645	813 985	715 369	218 952
Number of first readings of screening tests - per SSN - sampling - by general practitioner	114030-114041	yes	110 210	93 660	66 176	71 693	63 318	20 618
Number of first readings of screening tests - per SSN - sampling - by specialist	149612-149623	yes	1 081 826	877 655	605 469	742 292	652 051	198 334
Number of first readings of screening tests - per SSN - analysis	588350-588361	yes	1 249 878	999 840	710 015	872 452	765 049	223 200

(*) Maximum 1 test per SSN/woman reimbursed each two year after reimbursement modifications in 2009. Maximum 1 test per SSN/woman reimbursed each three year after reimbursement modifications in 2013. (§) Data of 2013 are incomplete since only data of the first six months 2013 are available.

Figure 56 – Proportion of screening samplings performed by a general practitioner or by a specialist (per year)



Remark: data of 2013 are incomplete since only data of the first six months 2013 are available.

Table 74 – Number of second readings of screening tests per year (analysis)

	Nomenclature	Unique SSN/year (*)	Year (§) 2009	2010	2011	2012	2013
Number of second readings of screening tests	588873-588884	no	12 288	27 279	33 739	31 247	8 943
Number of second readings of screening tests - per SSN	588873-588884	yes	12 258	27 174	33 674	31 211	8 942

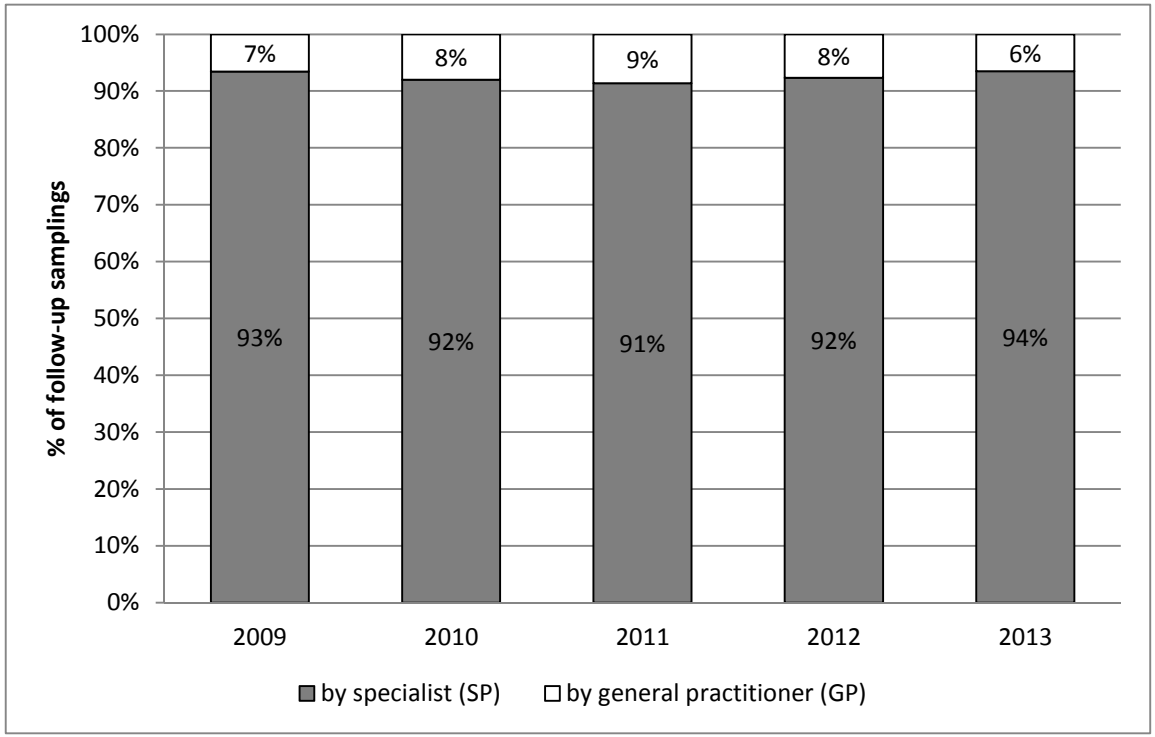
(*) Maximum 1 test per SSN/woman reimbursed each two year after reimbursement modifications in 2009. Maximum 1 test per SSN/woman reimbursed each three year after reimbursement modifications in 2013.
(§) No data for 2008 since nomenclature was created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Table 75 – Number of follow-up tests (sampling and analysis) per year

	Nomenclature	Unique SSN/year (*)	Year (§) 2009	2010	2011	2012	2013
Number of follow up tests - sampling - global	114170-114181 149634-149645	no	33 978	84 800	87 748	89 901	38 597
Number of follow up tests - sampling -by general practitioner	114170-114181	no	2 231	6 803	7 555	6 916	2 506
Number of follow up tests - sampling -by specialist	149634-149645	no	31 747	77 997	80 193	82 985	36 091
Number of follow up tests - per SSN - sampling - global	114170-114181 149634-149645	yes	33 540	75 813	78 241	80 045	38 161
Number of follow up tests - per SSN - sampling -by general practitioner	114170-114181	yes	2 220	6 565	7 290	6 639	2 498
Number of follow up tests - per SSN - sampling - by specialist	149634-149645	yes	31 320	69 248	70 951	73 406	35 663
Number of follow up tests – analysis	588895-588906	no	38 293	83 053	87 740	92 271	33 652
Number of follow up tests - per SSN - analysis	588895-588906	yes	37 529	73 175	77 280	80 972	33 332

(*) Maximum 2 tests per SSN/woman reimbursed per year after reimbursement modifications in 2009.
(§) No data for 2008 since nomenclature was created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Figure 57 – Proportion of follow-up samplings performed by a general practitioner or by a specialist (per year)



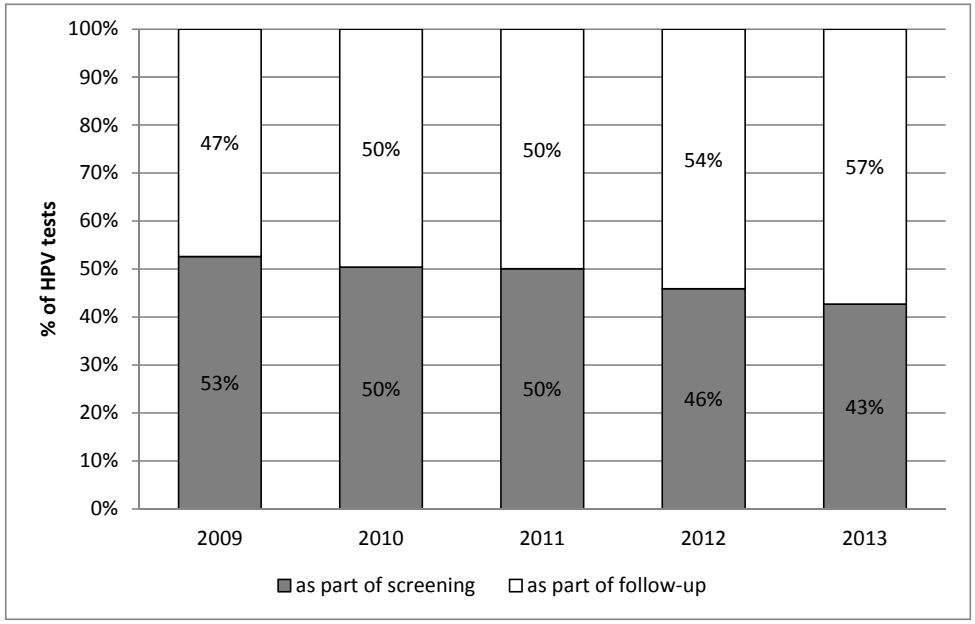
Remark: No data for 2008 since nomenclature was created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Table 76 – Number of HPV tests per year

	Nomenclature	Unique SSN/year	Year (§) 2009	2010	2011	2012	2013
Number of HPV tests as part of screening test (following abnormal screening test) (*)	588932-588943	no	8 488	19 759	23 229	21 789	6 685
Number of HPV tests as part of screening test (following abnormal screening test) - per SSN	588932-588943	yes	8 350	19 638	23 200	21 766	6 676
Number of HPV tests as part of follow-up examination (**)	588954-588965	no	7 649	19 464	23 192	25 680	8 968
Number of HPV tests as part of follow-up examination - per SSN	588954-588965	yes	7 445	17 994	21 435	23 725	8 930

(*) Maximum 1 test per SSN/woman reimbursed each two year after reimbursement modifications in 2009. Maximum 1 test per SSN/woman reimbursed each three year after reimbursement modifications in 2013.
(**) Maximum 2 tests per SSN/woman reimbursed per year after reimbursement modifications in 2009.
(§) No data for 2008 since nomenclature was created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Figure 58 – Proportion of HPV tests performed as part of screening or follow-up examinations (per year)



Remark: No data for 2008 since nomenclature was created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Table 77 – Number of colposcopies, further diagnoses and/or treatments per year

	Nomenclature (*)	Unique SSN/year	Year (§) 2008	2009	2010	2011	2012	2013
Number of colposcopies	COLPOSCOPY	no	360 321	327 432	279 098	281 231	269 716	51 644
Number of colposcopies - per SSN/year	COLPOSCOPY	yes	322 690	296 499	252 675	254 673	244 085	48 954
Number of further diagnoses and/or treatments, excluding colposcopies	FURTHER DIAGN/ TREATMENT	no	46 532	45 635	44 767	45 536	45 065	17 341
Number of further diagnoses and/or treatments, excluding colposcopies - per SSN/year	FURTHER DIAGN / TREATMENT	yes	44 990	44 277	43 289	44 151	43 648	17 166
Number of further diagnoses and/or treatments, including colposcopies	COLPOSCOPY & FURTHER DIAGN / TREATMENT	no	406 853	373 067	323 865	326 767	314 781	68 985
Number of further diagnoses and/or treatments, including colposcopies - per SSN/year	COLPOSCOPY & FURTHER DIAGN / TREATMENT	yes	367 680	340 776	295 964	298 824	287 733	66 120
Number of additional examinations	EXTRA	no	54 305	53 594	52 020	51 193	50 039	18 713
Number of additional examinations - per SSN/year	EXTRA	yes	52 376	51 836	50 060	49 119	47 937	18 238

(*) Nomenclature codes – and their respective meanings – that correspond to each category can be found in Appendix 1.2
(§) Data of 2013 are incomplete since only data of the first six months 2013 are available.

Appendix 1.1.2.3. Number of successive further investigations that follow screening tests

Introduction

In order to analyze the number of successive investigations that follow a screening test, the maximal time delay between the medical act(s) and the screening test had to be determined. The chosen time delays are shown in Table 78 and are based on the frequency of the time delay between the medical acts in question for a same SSN (see Appendix 1.4). Since the total number of samplings of a screening test is lower than the total number of first readings of a screening test, the date of the first reading was considered as the start point to calculate the maximal time delays.

Table 78 – Maximal time delay between two medical acts included in the analyses

	Nomenclature	Time delay
From a first reading of a screening test to a second reading of a screening test	588350-588361 combined with 588873-588884	0 - 30 days
From a first reading of a screening test to a HPV test (following abnormal screening test)	588350-588361 combined with 588932-588943	0 - 30 days
From a second reading of a screening test to a HPV test (following abnormal screening test)	588873-588884 combined with 588932-588943	0 - 30 days
From a first reading of a screening test to a colposcopy	588350-588361 combined with 431955-431966	1 - 365 days (*)
From a HPV test (following abnormal screening test) to a colposcopy	588932-588943 combined with 431955-431966	1 - 365 days (*)
From a first reading of a screening test to the first further diagnosis or treatment	588350-588361 combined with the first FURTHER DIAGN/TREAT	0 - 365 days

(*) Because a high number of colposcopies are performed on the same day as the first reading of a screening test (as part of screening tests), our analyses did not take into account the colposcopies performed on the same day as first readings or as HPV tests (time delay that equals 0).

Analysis of screening tests

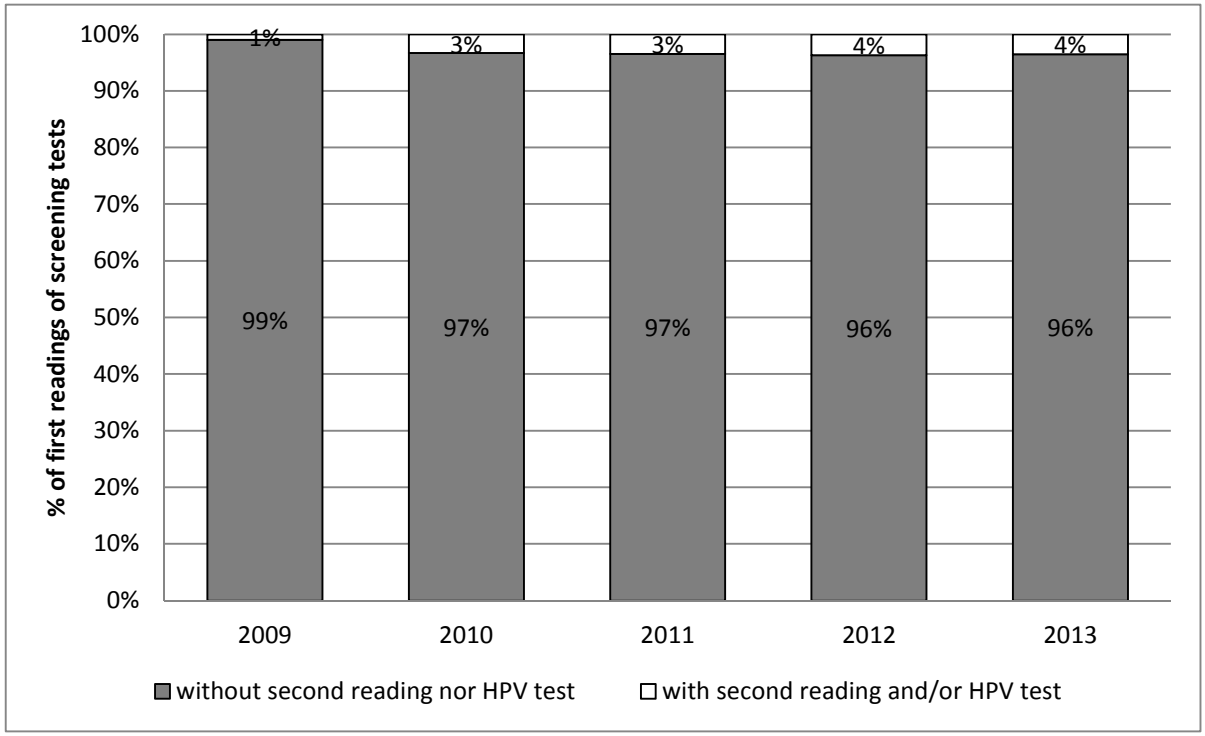
Table 79 and Figure 59 present the number and percentages of first readings of screening tests followed or not by a further examination within 30 days. This further examination can be either a second reading and/or a HPV test (performed as part of screening test).

Table 79 – Analysis of reimbursed first readings of screening tests (per year)

	Year (§) Raw number					Year (§) Percentages				
	2009	2010	2011	2012	2013 (*)	2009	2010	2011	2012	2013 (*)
Number of first readings of screening tests	1 022 976	712 950	875 098	766 912	223 226	100.0%	100.0%	100.0%	100.0%	100.0%
Number of first readings of screening tests	1 012 798	689 307	844 754	738 514	215 299	99.0%	96.7%	96.5%	96.3%	96.4%
without second reading (<= 30 d after first reading)										
nor HPV test (<= 30 d after first reading)										

(*) Records with a first reading performed between the 1st June 2013 and the 30th June 2013 were removed for the analysis (N= 93) to allow a better accuracy of results in 2013 (since a time delay of 30 days was chosen to consider that the second reading or the HPV test followed the first reading).
(§) No data for 2008 since nomenclature for second reading and HPV test were created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Figure 59 – Proportion of reimbursed first readings of screening tests followed or not by a further investigation (per year)



The number of first readings of screening tests with a further investigation is evaluated in more details in Table 80 and Figure 60. The further investigation can be a second reading, a HPV test or both.

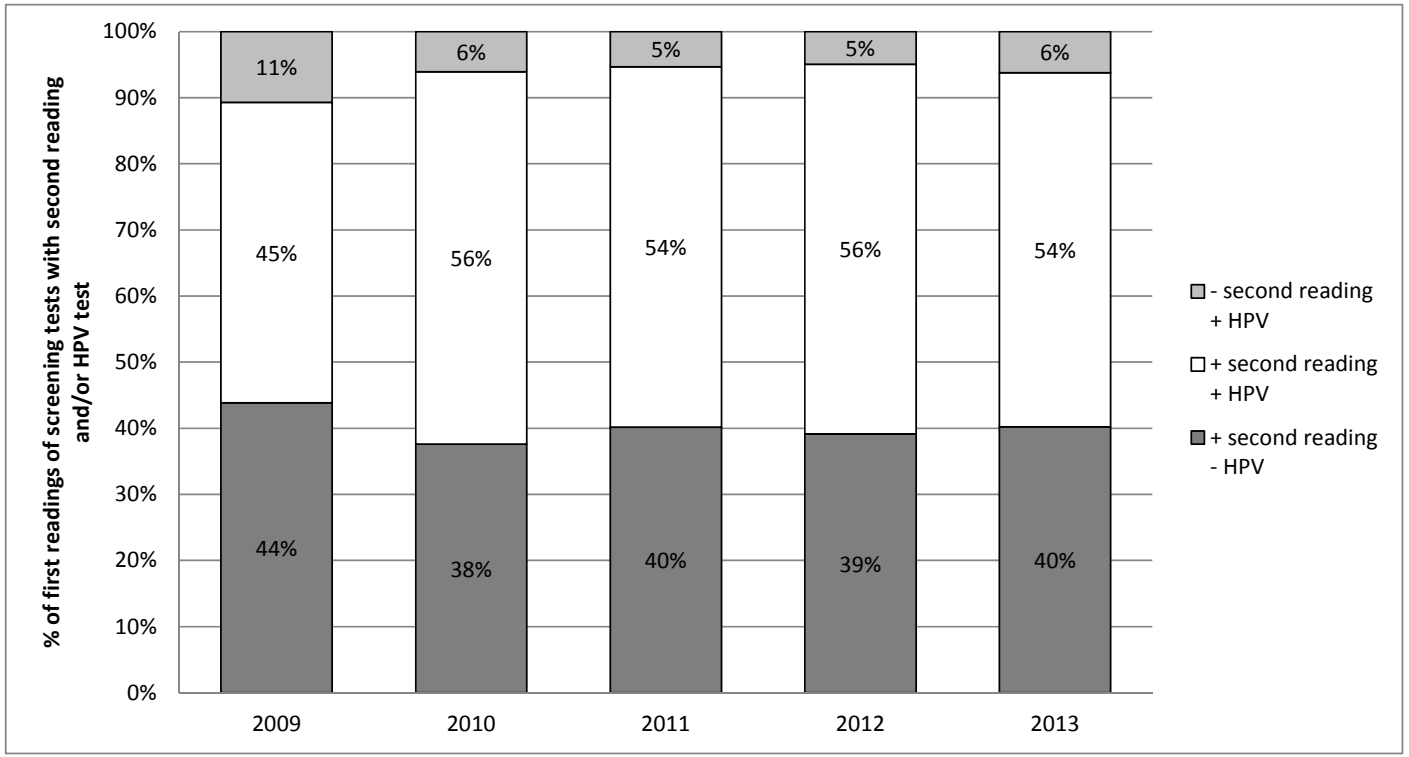
From 2010 to 2013, between 3-4% of the first readings of screening tests had a further investigation consisting of either a second reading, or a HPV test, or both. Of these samples with a further investigation, 45 – 56% had a second reading and a HPV test; 38 – 44% had no HPV test.

Table 80 – Analysis of reimbursed first readings of screening tests followed by a further investigation (per year)

	Year (§) Raw number					Year (§) Percentages				
	2009	2010	2011	2012	2013(*)	2009	2010	2011	2012	2013(*)
Number of first readings of a screening test	10 178	23 644	30 344	28 396	7 927	100.0%	100.0%	100.0%	100.0%	100.0%
+ second reading of a screening test (<= 30 d after first reading)										
or + HPV test that follows abnormal screening test (<= 30 d after first reading)										
Number of first readings of a screening test	4 466	8 894	12 193	11 118	3 189	43.9%	37.6%	40.2%	39.2%	40.2%
+ second reading of a screening test (<= 30 d after first reading)										
without HPV test that follows abnormal screening test (<= 30 d after first reading)										
Number of first readings of a screening test	1 091	1 435	1 622	1 403	492	10.7%	6.1%	5.3%	4.9%	6.2%
without second reading of a screening test (<= 30 d after first reading)										
+ HPV test that follows abnormal screening test (<= 30 d after first reading)										
Number of first readings of a screening test	4 621	13 314	16 529	15 877	4 246	45.4%	56.3%	54.5%	55.9%	53.6%
+ second reading of a screening test (<= 30 d after first reading)										
+ HPV test that follows abnormal screening test (<= 30 d after first reading)										

(*) Records with a first reading performed between the 1st June 2013 and the 30th June 2013 were removed for the analysis (N= 93) to allow a better accuracy of results in 2013 (since a time delay of 30 days was chosen to consider that the second reading or the HPV test followed the first reading).
(§) No data for 2008 since nomenclature for second reading and HPV test were created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

Figure 60 – Analysis of reimbursed first readings of screening tests followed by a second reading and/or a HPV test



Remark: No data for 2008 since nomenclature for second reading and HPV test were created in 2009. Data of 2013 are incomplete since only data of the first six months 2013 are available.

For the first readings that are followed by a second reading and a HPV test, it was evaluated whether these samples were also followed by a colposcopy or a further diagnosis/treatment (Table 81, Figure 61).

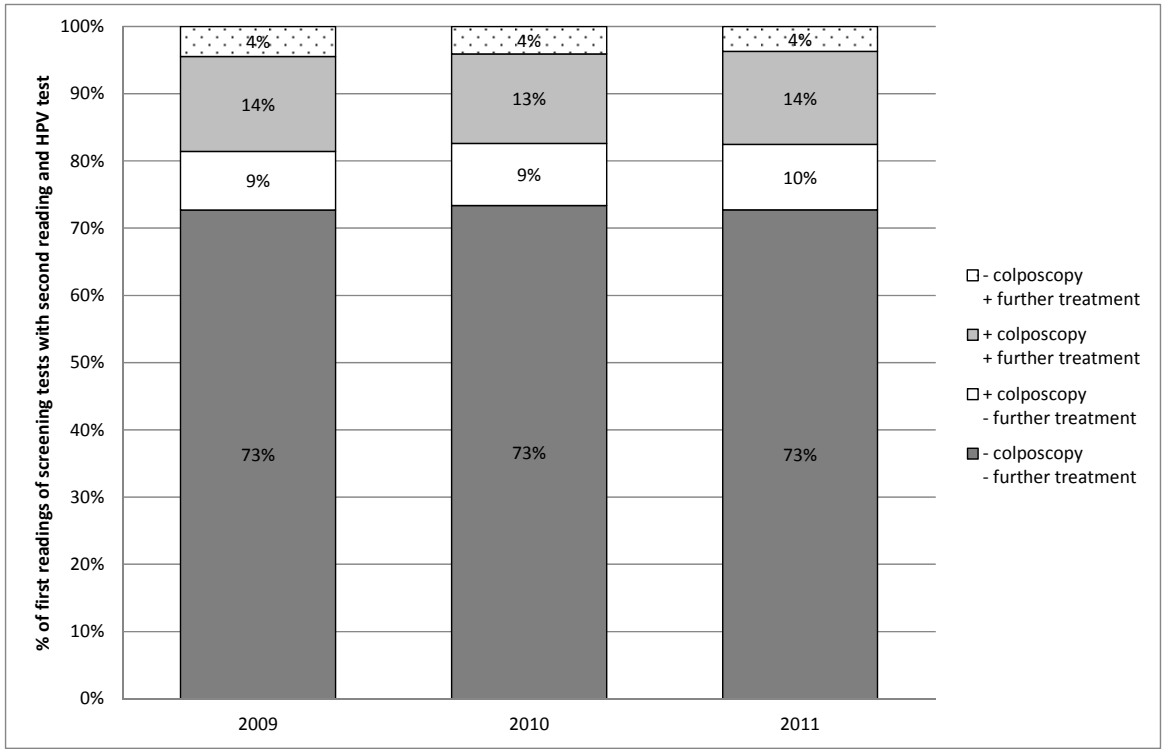
Between 72-74% of the first readings of screening tests, which were followed by a second reading and a HPV test, were neither followed by a colposcopy nor by a further diagnosis/treatment during one year after the screening test. Between 27 - 28% of these screening tests were followed by a colposcopy (followed or not by a further diagnosis/treatment) during one year after the screening test.

Table 81 – Analysis of reimbursed first readings of screening tests followed by a colposcopy and/or a further diagnosis/treatment (per year)

	Year (§) Raw number			Year (§) Percentages		
	2009	2010	2011	2009	2010	2011
Number of first readings of screening tests	4 621	13 314	16 529	100.0%	100.0%	100.0%
+ second reading (<= 30 d after first reading)						
+ HPV test (that follows abnormal screening test) (<= 30 d after first reading)						
Number of first readings of screening tests	3 360	9 768	12 024	72.7%	73.4%	72.7%
+ second reading (<= 30 d after first reading)						
+ HPV test (that follows abnormal screening test) (<= 30 d after first reading)						
without **colposcopy (> 0 d and <= 365 d after first reading)**						
without **further diagnosis/treatment (<= 365 d after first reading)**						
Number of first readings of screening tests	403	1 232	1 609	8.7%	9.3%	9.7%
+ second reading (<= 30 d after first reading)						
+ HPV test (that follows abnormal screening test) (<= 30 d after first reading)						
+ colposcopy (> 0 d and <= 365 d after first reading)						
without **further diagnosis/treatment (<= 365 d after first reading)**						
Number of first readings of screening tests	652	1 772	2 285	14.1%	13.3%	13.8%
+ second reading (<= 30 d after first reading)						
+ HPV test (that follows abnormal screening test) (<= 30 d after first reading)						
+ colposcopy (> 0 d and <= 365 d after first reading)						
+ further diagnosis/treatment (<= 365 d after first reading)						
Number of first readings of screening tests	206	542	611	4.5%	4.1%	3.7%
+ second reading (<= 30 d after first reading)						
+ HPV test (that follows abnormal screening test) (<= 30 d after first reading)						
without **colposcopy (> 0 d and <= 365 d after first reading)**						
+ further diagnosis/treatment (<= 365 d after first reading)						

(§) No data for 2008 since nomenclature for second reading and HPV test were created in 2009.
No data for 2012 since only data of the first six months 2013 are available and a time delay of 365 days is needed after the date of the screening test.

Figure 61 – Proportion of screening tests followed by a colposcopy and/or a further diagnosis/treatment (per year)



Remark: No data for 2008 since nomenclature for second reading and HPV test were created in 2009.
No data for 2012 since only data of the first six months 2013 are available and a time delay of 365 days is needed after the date of the screening test.

Table 82 shows the nature and proportion of all the further diagnoses/treatments that follow screening tests (first readings followed by a second reading and a HPV test).

Table 82 – Nature and proportion of further diagnoses/treatments performed between 2009-2013 that followed a screening test (first reading followed by a second reading and a HPV test)

Further treatment	Nomenclature	Raw numbers	Percentages
Biopsy	432110-432121	7637	64.9%
Conisation	432294-432305	2743	23.3%
Hysterectomy	431270-431281 431314-431325 431336-431340 431351-431362 432670-432681 432736-432740	823	7.0%
Polypectomy	149052-149063	151	1.3%
Amputation	431491-431502	410	3.5%
Other	431911-431922 432154-432165	9	0.1%

Note: The analysis takes into account all further diagnoses/treatments performed after screening tests, without distinguishing possible combinations performed after a same screening test.

Analysis of follow-up tests

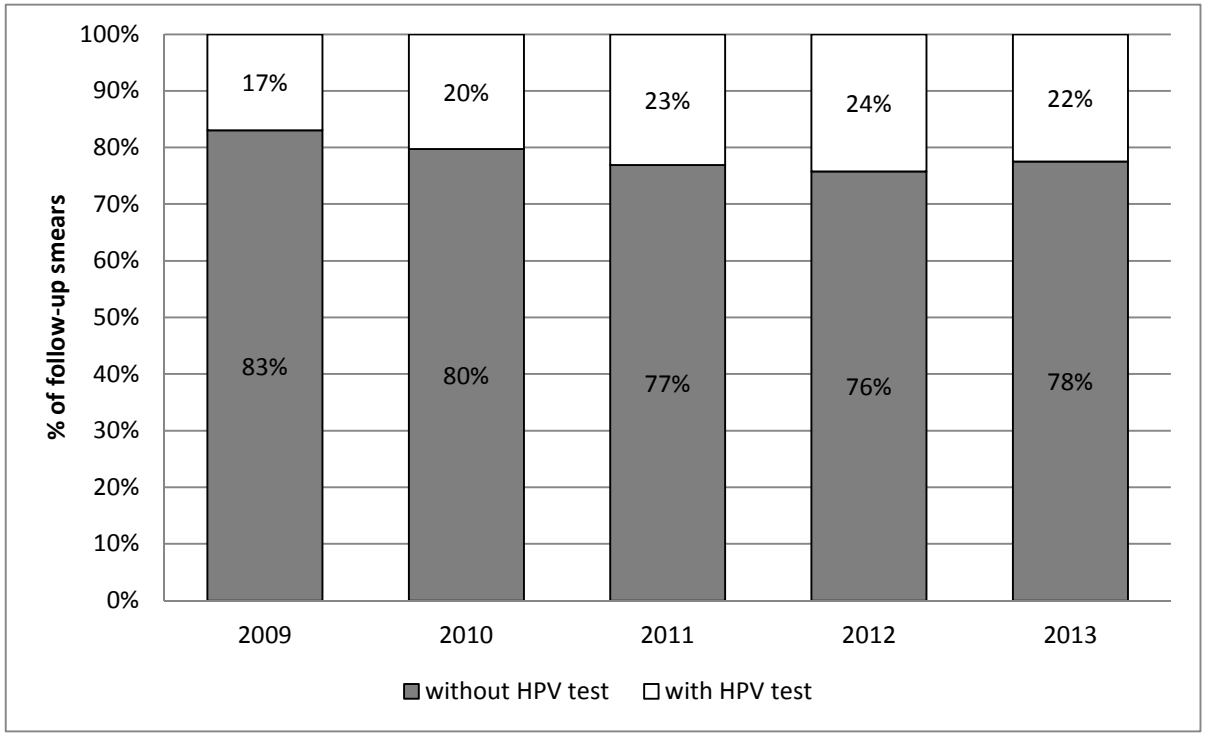
Table 83 and Figure 62 give the number and percentage of follow-up smears followed or not by a HPV test (which is performed in the context of follow-up).

Table 83 – Analysis of reimbursed follow-up smears (per year)

	Year (§)					Year (§)				
	Raw numbers					Percentages				
	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*
Number of follow-up smears	38 293	83 053	87 740	92 271	33 633	100.0%	100.0%	100.0%	100.0%	100.0%
Number of follow-up smears **without** HPV test (as part of follow-up examination) (<= 30 d after follow-up smear)	31 793	66 212	67 498	69 906	26 071	83.0%	79.7%	76.9%	75.8%	77.5%
Number of follow-up smears + HPV test (as part of follow-up examination) (<= 30 d after follow-up smear)	6 500	16 841	20 242	22 365	7 562	17.0%	20.3%	23.1%	24.2%	22.5%

(*) Records with a follow-up smear performed between the 1st June 2013 and the 30th June 2013 were removed for the analysis (N= 19) to allow a better accuracy of results in 2013 (since a time delay of 30 days was chosen to consider that the HPV test followed the follow-up smear).
(§) No data for 2008 since nomenclature for second reading and HPV test were created in 2009.
Data of 2013 are incomplete since data of only the first six months 2013 are available.

Figure 62 – Proportion of follow-up smears followed by a HPV test (per year)



Remark: No data for 2008 since nomenclature for second reading and HPV test were created in 2009.
Data of 2013 are incomplete since data of only the first six months 2013 are available.

Table 84 shows that the number of follow-up smears performed per year is high and considerably higher that the number of first readings that are followed by a second reading and a HPV test. It was therefore analyzed in which conditions those follow-up smears were performed, i.e. after which medical acts the follow-up smears were performed. Table 84 below shows that between 26.5% and 34.7% of the follow-up smears were not preceded by any other medical act in a one year period. In this analysis all medical acts corresponding to the nomenclature codes listed in Table 71 and Table 72 were taken in to account, except the codes classified in the category 'EXTRA' in Table 72.

Table 84 – Number of reimbursed follow-up smears (analysis) preceded or not (1-365 days) by another medical act

	Raw numbers					Percentages				
	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Number of follow-up smears	38 293	83 053	87 740	92 271	33 652	100.0%	100.0%	100.0%	100.0%	100.0%
- not preceded by any other medical act	10 161	25 586	25 198	27 221	11 674	26.5%	30.8%	28.7%	29.5%	34.7%
- preceded by a first reading of a screening test only	13 373	12 259	9 956	9 739	3 189	34.9%	14.8%	11.3%	10.6%	9.5%
- preceded by another follow-up smear only	83	5 547	7 538	8 100	3 219	0.2%	6.7%	8.6%	8.8%	9.6%
- preceded by a first reading of a screening test and a colposcopy only	5 622	4 587	3 866	3 439	937	14.7%	5.5%	4.4%	3.7%	2.8%
- preceded by a colposcopy only	1 488	3 975	4 351	4 370	1 227	3.9%	4.8%	5.0%	4.7%	3.6%
- preceded by a first reading, a colposcopy and a further treatment only	4 601	3 444	2 112	1 858	565	12.0%	4.1%	2.4%	2.0%	1.7%
- preceded by a HPV test performed as part of a follow-up examination only	34	2 213	3 806	4 432	1 817	0.1%	2.7%	4.3%	4.8%	5.4%
- preceded by a first reading, a second reading and a HPV test only	106	2 280	3 625	4 167	1 351	0.3%	2.7%	4.1%	4.5%	4.0%
- preceded by another follow-up smear and a colposcopy only	38	2 556	3 456	4 012	1 359	0.1%	3.1%	3.9%	4.3%	4.0%
- preceded by another follow-up smear, a colposcopy and a further treatment only	28	2 688	3 648	3 601	1 272	0.1%	3.2%	4.2%	3.9%	3.8%
- preceded by another (combination of) medical act(s)	2 759	17 918	20 184	21 332	7 042	7.2%	21.6%	23.0%	23.1%	20.9%

Analysis of colposcopies

When calculating the maximal time delay between a first reading of a screening test and a colposcopy, it was noticed that a high number of colposcopies were performed on the same day than the first reading.

After a more detailed analysis, it was even noticed that a lot of colposcopies were performed a few days before the first reading, actually on the same day than the sampling. This is illustrated in Figure 63.

Interestingly, Table 85 shows that the percentage of colposcopies performed as part of screening test (i.e. at the same time than a cervix smear) tends to decrease between 2009 and 2013.

Table 86 presents the number of colposcopies preceded or not by a cervix smear. Between 77% and 85% of colposcopies were not preceded by a cervix smear in a one year period. These high percentages can be explained by the fact that most of colposcopies were performed as part of screening test.

Figure 63 – Time delay between a colposcopy and the next screening (sampling and first reading)

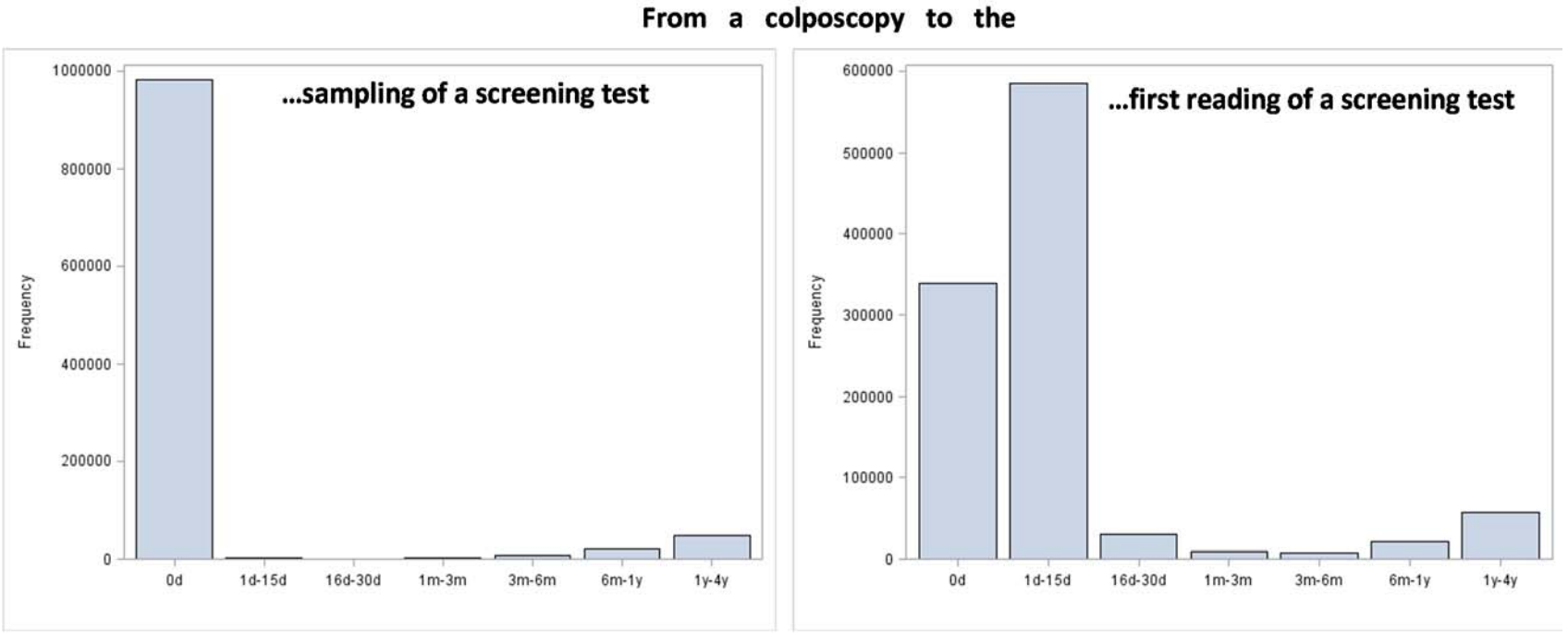


Table 85 – Number of reimbursed colposcopies performed on the same day than the sampling of a cervix smear (per year)

	Year (§) Raw numbers					Year (§) Percentages				
	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Number of colposcopies	327 432	279 098	281 231	269 716	51 644	100.0%	100.0%	100.0%	100.0%	100.0%
Number of colposcopies performed on the same day than a sampling of a screening test	233 030	131 719	158 541	133 681	11 938	71.2%	47.2%	56.4%	49.6%	23.1%

(§) Data of 2013 are incomplete since data of only the first six months 2013 are available.

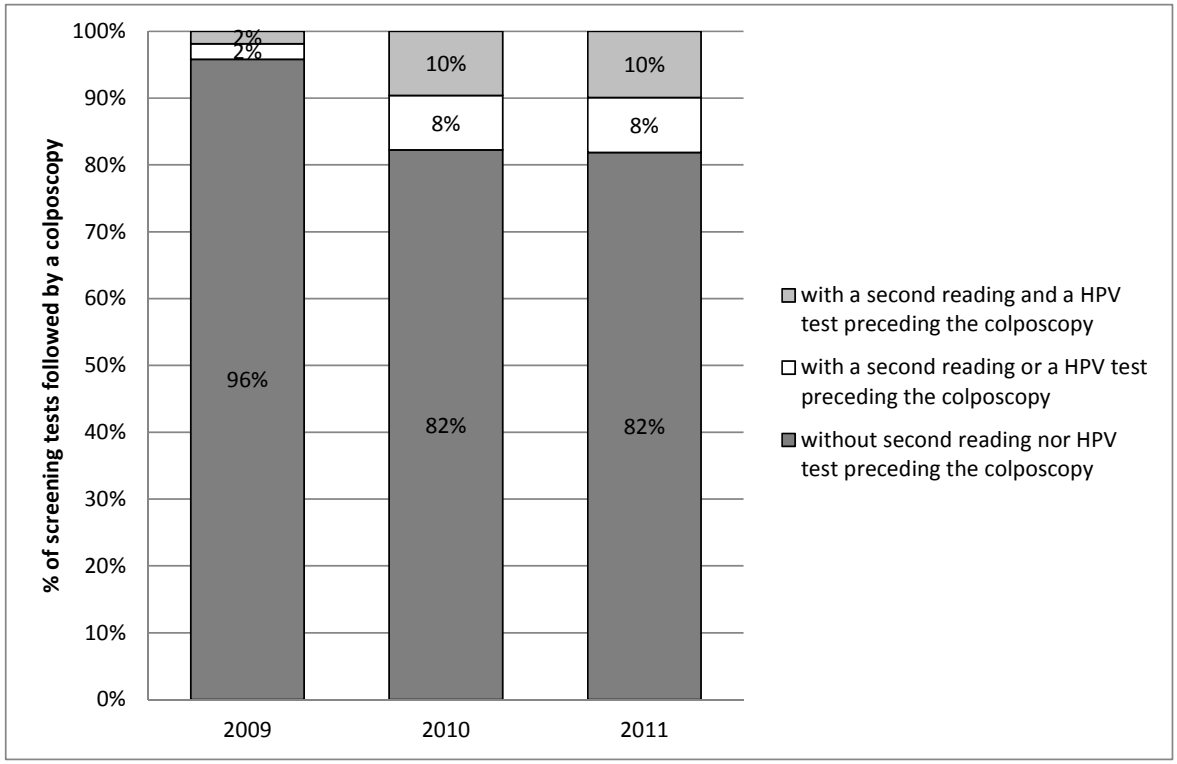
Table 86 – Number of reimbursed colposcopies preceded or not by the first reading of a cervix smear (per year)

	Year (§) Raw numbers					Year (§) Percentages				
	2009	2010	2011	2012	2013	2009	2010	2011	2012	2013
Number of colposcopies	327 432	279 098	281 231	269 716	51 644	100.0%	100.0%	100.0%	100.0%	100.0%
Number of colposcopies without **any previous cervix smear (> 0 d en <= 365 d before colposcopy)**	252 592	228 085	237 826	223 300	39 620	77.1%	81.7%	84.6%	82.8%	76.7%
Number of colposcopies + at least one previous cervix smear (> 0 d en <= 365 d before colposcopy)	74 840	51 013	43 405	46 416	12 024	22.9%	18.3%	15.4%	17.2%	23.3%

(§) Data of 2013 are incomplete since data of only the first six months 2013 are available.

When the first reading of a screening test is really followed by a colposcopy (i.e. the colposcopy is not performed on the same day but in the year that follows the first reading), it is noticed that for most cases (between 82% and 96%) no second reading nor HPV test preceded the colposcopy (Figure 64).

Figure 64 – Analysis of first readings of screening tests followed by a colposcopy



Remark: No data for 2008 since nomenclature for second reading and HPV test were created in 2009.
No data for 2012 since only the first six months 2013 are available and a time delay of 356 days after the date of the first reading is needed.

Analysis of further diagnoses/treatments

When calculating the maximal time delay between a first reading of a screening test and a further diagnosis/treatment, it was also noticed that some treatments were performed on the same day than the first reading. It mainly concerned polypectomies and biopsies.

Table 87 below shows that the cases where a polypectomy or a biopsy is performed on the same day than a screening sampling are much less frequent than the cases where a colposcopy is performed simultaneously than a screening sampling.

Table 87 – Number of screening samplings performed on the same day than a colposcopy, a polypectomy or a biopsy

	Year (§)					
	Raw numbers					
	2008	2009	2010	2011	2012	2013
Number of screening samplings	1 264 346	995 983	673 983	816 284	717 169	219 095
Number of screening samplings performed on the same day than a colposcopy	312 559	233 030	131 719	158 541	133 681	11 938
Number of screening samplings performed on the same day than a polypectomy	2 737	2 302	1 691	1 987	1 785	577
Number of screening samplings performed on the same day than a biopsy	7 896	5 040	1 870	1 956	1 508	368

(§) Data of 2013 are incomplete since data of only the first six months 2013 are available.

Appendix 1.1.3. Global overview of laboratory characteristics

Appendix 1.1.3.1. Overview of analyses performed per laboratory (based on IMA data)

The IMA database contains 5 545 512 records with a nomenclature code that indicates an analysis by a laboratory (Table 88); i.e. one of the following nomenclature codes:

- Cytological tests:
  - 588350-588361: first reading of screening tests – analysis
  - 588873-588884: second reading of screening tests – analysis
  - 588895-588906: follow-up smears – analysis
- HPV tests:
  - 588932-588943: HPV tests that follow abnormal screening test
  - 588954-588965: HPV tests as part of follow-up examinations

Table 88 – Number of analyses performed by laboratories in the IMA database

	Nomenclature code	2008-2013*
Cytological tests:	588350-588361	5 380 471
first reading of screening test – analysis	588873-588884	
second reading of screening tests – analysis	588895-588906	
follow-up smears – analysis		

HPV tests:	588932-588943	165 041
HPV tests as part of screening test	588954-588965	
HPV tests as part of follow-up examination		
	Total	**5 545 512**

** These results were obtained on the full IMA database (not cleaned up from duplicate records).*

Some of these records (N= 31 668) had no laboratory code or had an invalid laboratory code. These records were removed from the database before performing further analyses.

After this data cleaning step, the database contained records from 361 different known laboratories. 145 laboratories had performed less than 20 analyses between 2008 and 2013. Since the contribution of these 145 laboratories is not substantial, they were not taken into account for further analyses.

Table 89 gives the number of laboratories that performed cytological tests and/or HPV tests per year.

Table 89 – Number of laboratories that performed cytological tests and/or HPV tests per year

Type of laboratory	Year*					
	2008	2009	2010	2011	2012	2013
Cytology only	183	138	128	135	126	116
Cytology & HPV	0	50	53	45	46	35
HPV only	0	3	7	4	6	9

** These results were obtained on the full IMA database (not cleaned up from duplicate records). The 145 laboratories having performed less than 20 analyses between 2008 and 2013 were not taken into account.*

In response to the Royal Decree of 5/12/2011 regarding the recognition of laboratories for pathological anatomy, a total of 105 central laboratories and 137 activity centers has submitted an application for recognition to the WIV/ISP in early 2013.

Appendix 1.1.3.2. Overview of methodology used in individual laboratories

Table 90, Table 91, Table 92, Table 93, Table 94 below give information on the methodology used by laboratories to analyze smears and to perform HPV tests. This information was obtained by the BCR from the laboratories for pathological anatomy for years 2011-2013. The most recent known data for these years are reported in the tables below.

Table 90 – Method used to analyze smears per region and for Belgium (2011-2013)

	BRUSSELS		FLANDERS		WALLONIA		BELGIUM	
METHOD USED TO ANALYZE SMEARS	TOTAL (N)	%	TOTAL (N)	%	TOTAL (N)	%	TOTAL (N)	%
Liquid based	5	45.5%	49	81.7%	6	30.0%	60	65.9%
Liquid based (99%) + Conventional (1%)	1	9.1%	-	-	1	5.0%	2	2.2%
Liquid based (95%) + Conventional (5%)	1	9.1%	2	3.3%	1	5.0%	4	4.4%
Liquid based (50%) + Conventional (50%)	1	9.1%	-	-	-	-	1	1.1%
Liquid based (x%) + Conventional (x%)	3	27.3%	1	1.7%	3	15.0%	7	7.7%
Conventional	-	-	1	1.7%	6	30.0%	7	7.7%
Not applicable (*)	-	-	3	5.0%	-	-	3	3.3%
Unkown	-	-	4	6.7%	3	15.0%	7	7.7%
TOTAL NUMBER OF PATHOLOGY LABORATORIES	**11**	**100.0%**	**60**	**100.0%**	**20**	**100.0**	**91**	**100.0%**

(*) 3 laboratories only analyze cervical biopsies, but no cervical smears.

Table 91 – Which laboratory performs HPV tests? (2011-2013)

WHICH LABORATORY PERFORMS HPV TESTS	Number of laboratories	%
HPV test are performed in pathology laboratory itself	20	22.0%
HPV tests sent to another pathology laboratory	27	29.7%
HPV tests sent to a clinical laboratory relied to the same hospital as the pathology laboratory	17	18.7%
HPV tests sent to another clinical laboratory	16	17.6%
Number of pathology laboratory that did not respond	8	8.8%
Not applicable (*)	3	3.3%
TOTAL NUMBER OF PATHOLOGY LABORATORIES	**91**	**100.0%**

(*) 3 laboratories only analyze cervical biopsies, but no cervical smears.

Table 92 – Type of laboratory that performs the HPV tests (2011-2013)

TYPE OF LABORATORY THAT PERFORMS THE HPV TESTS	Number of laboratories	%
Number of pathology laboratories that perform HPV tests	21	53.8
Number of clinical laboratories that perform HPV tests	18	46.2
TOTAL	39	100.0

Table 93 – Overview of the different tests that are used to detect HPV and the high risk HPV types that are detected by each test (2011-2013)

Firm	Type of HPV test used	Number of laboratories that use the test	Detection and / or genotyping of high risk HPV genotypes	Detection and / or genotyping of other (non high risk) HPV genotypes
Qiagen	digene HC2 HR HPV DNA test	20	detection of HR HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68	no
Abbott	Abbot RealTime HR HPV	22	detection of HR HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68; genotyping of HPV 16 and 18	HPV type 66 (probably high risk)
Roche		15	-	-
	Amplicor	1	detection of HR HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68	no
	Cobas	7	detection of HR HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68; specific genotyping of HPV 16 and 18	HPV type 66 (probably high risk)
	Linear array HPV genotyping test	7	detection and discrimination of HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68	24 other HPV types including: probably high risk: HPV 26, 55,62,66,71,73,82,83,84 low risk: 6,11,40,42,54,61,70,72,81 undetermined risk: 53,64,67,69,IS39, CP108
Hologic	Cervista HPV HR	4	detection of HR HPV types 16,18,31,33,35,39,45,51,52,56, 58,59,68	HPV type 66 (probably high risk)
AML	AML probe	4	Unknown	unknown
DAKO	IHC types	2	detection of HR HPV types 6,11,16,18,31,33,51,52,56,58	HPV types 11 and 42 (low risk)
Greiner Bio One	PapilloCheck	2	genotyping of HPV types 16,18,31,33,35,39,45,51,52,56,58,59,68	HPV type 66 (probably high risk)
bioMérieux	NucliSENS EasyQ HPV	1	detection and discrimination of HR HPV types 16,18,31,33,45	unknown
Sacace Biotechnologies	HPV High Risk Screen Real-TM Quant	1	detection of HR HPV types 16,18,31,33,35,39,45,51,52,56,58,59	no
Abbott / AML		1	-	-
AML / Hologic		1	-	-
bioMérieux / Qiagen		1	-	-
Unknown		14	-	-
Not applicable(*)		3	-	-
	Total	**91**		

(*) 3 laboratories only analyze cervical biopsies, but no cervical smears.

Table 94 – Use of an automated analysis method (computer-assisted imaging assistance), per region (2011-2013)

	REGION			
	BRUSSELS	FLANDERS	WALLONIA	BELGIUM
Hologic, ThinPrep Imager	2	12	1	15
Becton Dickinson, BD FocalPoint™ Slide Profiler	-	1	-	1
No computer assisted	7	28	10	45
Unknown	2	16	9	27
Not applicable (*)	-	3	-	3
Total	11	60	20	91

(*) 3 laboratories only analyze cervical biopsies, but no cervical smears.

Appendix 1.1.4. Analysis of cyto-histo pathology register (CHP) coupled with the IMA database (year 2011)

In this section, the IMA data are coupled to the CHP. Thanks to this coupling, the diagnosis/result of cytological analyses and HPV tests registered in the IMA database will be known. Since the CHP currently contains data of 2011, only the medical acts performed in 2011 have been selected for coupling. CHP data are delivered by the anatomopathological laboratories and must be treated by BCR before any further analyses. Currently, not all CHP data of 2011 have been treated by BCR, and the CHP is consequently not exhaustive for 2011. On the total of 91 laboratories that had delivered data on cervical samples of 2011, data from 62 laboratories were processed and analyzed. These 62 laboratories were selected based on the quality of the data provided, especially on the percentage of reported HPV test results (in order to increase the exhaustivity of HPV tests in CHP). The IMA database was delivered to BCR in November 2013. At that time, reimbursements of medical acts for the year 2011 were nearly closed. Consequently, The IMA database can be almost considered as exhaustive for 2011.

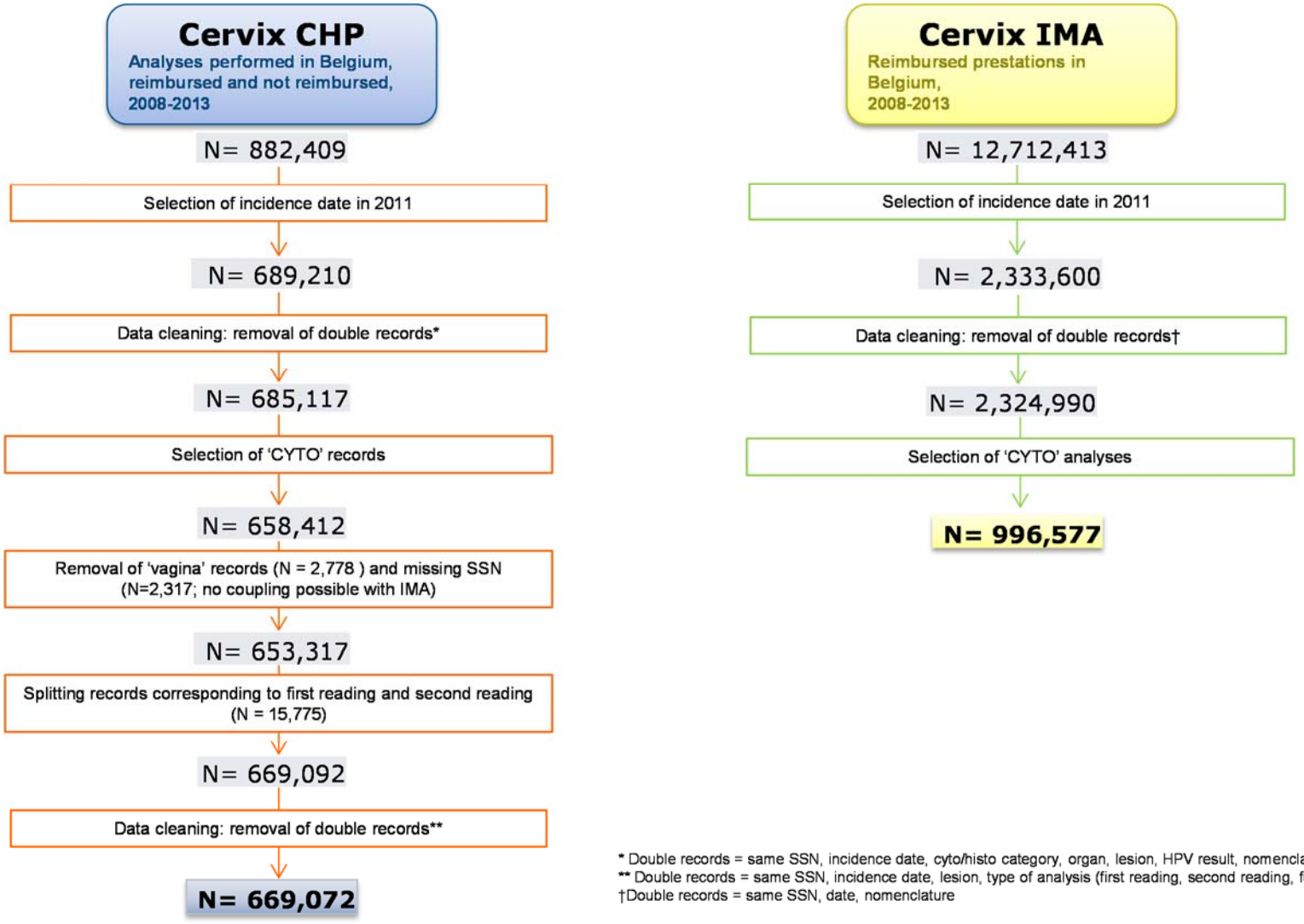
Appendix 1.1.4.1. Coupling of CHP and IMA data

Coupling of cytological analyses

Extraction of cytological analyses performed in 2011 from CHP and IMA data

Cytological analyses performed in 2011 were extracted from CHP and IMA database as described in Figure 65. There are 669,072 cytological analyses in the treated data of CHP for 2011 (i.e. data of the 62 selected laboratories), and 996,577 in the IMA database.

Figure 65 – Steps followed to extract the cytological analyses which were performed in 2011 from CHP (i.e. cytological analyses peformed by one of the 62 selected laboratories) and IMA data



* Double records = same SSN, incidence date, cyto/histo category, organ, lesion, HPV result, nomenclature
** Double records = same SSN, incidence date, lesion, type of analysis (first reading, second reading, follow-up)
†Double records = same SSN, date, nomenclature

Before coupling, cytological analyses from CHP and IMA data were categorized into the 3 following categories based on their nomenclature codes:

- First reading of screening test: 588350, 558361
- Second reading of screening test: 588873, 588884
- Follow-up smear: 588895, 588906

The CHP also contains two other types of medical acts that cannot be categorized in the 3 categories cited above, namely:

- medical acts that are clearly declared as 'not reimbursed' by laboratories. Those medical acts can theoretically not be coupled to IMA. Any coupling of these 'not reimbursed' medical acts with IMA will be consequently considered as incorrect.
- medical acts for which the laboratory did not deliver any nomenclature code or delivered an invalid/unspecific nomenclature code. It cannot be said whether those medical acts belong to the 'first reading', 'second reading', 'follow-up' or 'not reimbursed' category. Any coupling of these medical acts with IMA will be authorized. If such a CHP record can be coupled to an IMA record, the CHP record is categorized according to the IMA nomenclature code.

Coupling cytological analyses from CHP and IMA data

A cytological analysis from CHP database was coupled to a cytological analysis from IMA database when the following conditions were fulfilled:

- Both records have the same SSN;
- The difference between the reimbursement date (date from IMA) and the incidence date (date from CHP) is ± 15 days;
- There is no nomenclature conflict: both records belong to the same category of analysis (first reading/second reading/follow-up) or the nomenclature code of the CHP record is not declared, invalid or unspecific. However, if both records do not belong to the same category of analysis or if the CHP record is declared as not reimbursed, records are not coupled.

The outcome of the coupling of cytological analyses from CHP and IMA database are described in Figure 12. A total of 557 918 records are coupled. If we consider that the IMA database is exhaustive for reimbursed medical acts of 2011 (i.e. that there is a total of 999 557 reimbursed cytological analyses in 2011), this means that by selecting 62 out of the 91 laboratories about 56.0% of all reimbursed samples are treated.

It is worth noticing that 16.6% of CHP records (111 154 / 669 072) are not coupled to any IMA record, though most of them (11.5%) are declared as reimbursed. Several reasons can explain the origin of these CHP records declared as reimbursed but not coupled to any IMA record:

1. The nomenclature code of CHP records have been wrongly declared by the laboratories;
2. The records have not yet any corresponding IMA record because of a delay in the registration of IMA data.

The proportion of non-reimbursed cytological analyses (=overconsumption) is comprised between:

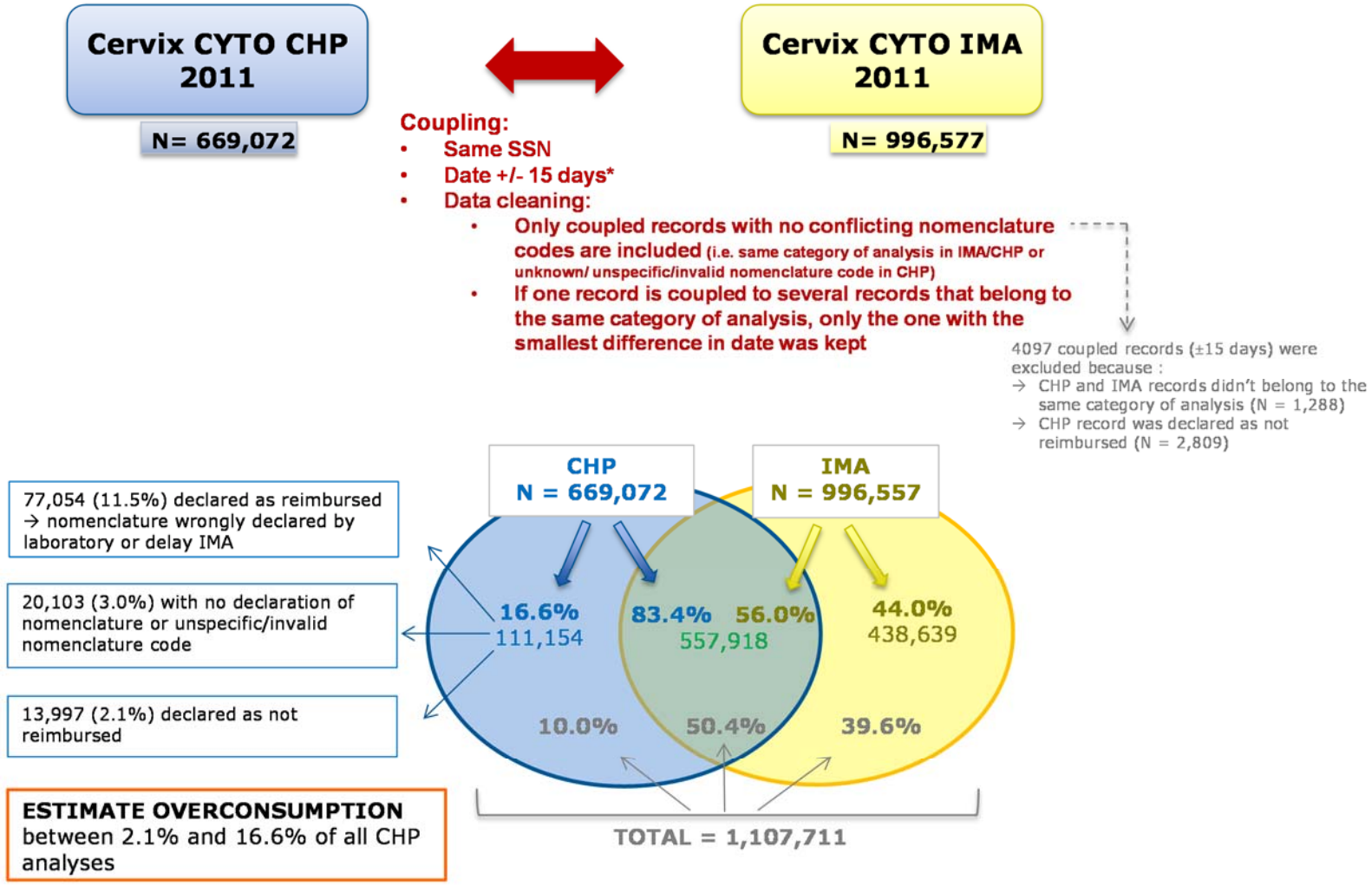
- 2.1%, which is the number of CHP records clearly declared as not reimbursed by laboratories;
- and 16.6%, in the case where all the CHP records that are not coupled to IMA, whatever they are declared reimbursed by laboratories (11.5%) or they have an invalid nomenclature code (3.0%), are actually not reimbursed.

Note: the total number of cytological medical acts (reimbursed and not reimbursed) of 2011 is unknown:

1. the IMA data only contain reimbursed medical acts;
2. the CHP is not exhaustive for 2011 since only 62 of 91 laboratories that had delivered data are included in this study;
3. the CHP contains analyses for which the reimbursement status is unknown (because not declared or wrongly declared by laboratories).

However, by adding the two databases the total number of cytological medical acts performed in Belgium in 2011 is estimated at this moment to 1 107 711 (see Figure 66).

Figure 66 – Coupling cytological analyses (performed in 2011) from CHP and IMA data



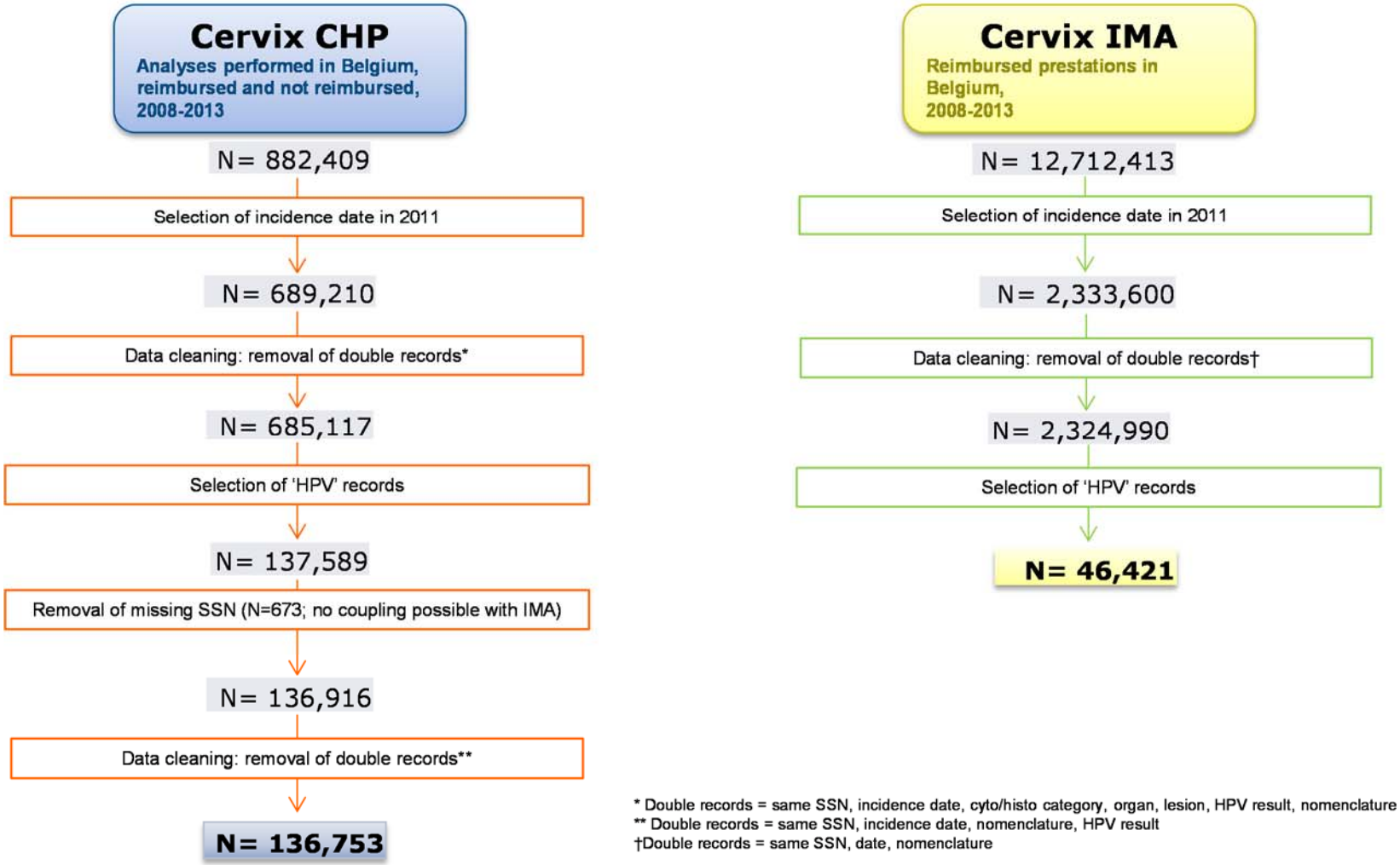
* 15 days was arbitrarily chosen as coupling criterion to allow small differences in prestation dates between CHP and IMA

Coupling of HPV tests

Extraction of HPV tests performed in 2011 from CHP and IMA data

HPV tests performed in 2011 were extracted from CHP and IMA database as described in Figure 67. There are 136 753 HPV tests in the treated data of CHP for 2011, and 46 421 in the IMA database. On the total of 91 laboratories that had delivered data on cervical samples of 2011, data from 62 laboratories were processed and analyzed. These 62 laboratories were selected based on the quality of the data provided, especially on the percentage of reported HPV test results in order to increase the exhaustivity of HPV tests in CHP.

Figure 67 – Steps followed to extract HPV tests performed in 2011 from the CHP (i.e. HPV tests performed by one the 62 selected laboratories) and IMA data



* Double records = same SSN, incidence date, cyto/histo category, organ, lesion, HPV result, nomenclature
** Double records = same SSN, incidence date, nomenclature, HPV result
†Double records = same SSN, date, nomenclature

Before coupling, HPV tests were categorized into the 2 following categories based on their nomenclature codes:

- HPV tests performed as part of a screening test: 588932, 588943
- HPV tests performed as part of a follow-up examination: 588954, 588965

The CHP also contains two other types of HPV tests that cannot be categorized in the 2 categories cited above, namely:

- HPV tests that are clearly declared as 'not reimbursed' by laboratories. Those tests can theoretically not be coupled to IMA. Any coupling of these HPV tests with IMA will be consequently considered as incorrect.
- HPV tests for which the laboratory did not deliver any nomenclature code or delivered an invalid/unspecific nomenclature code. For those tests, it cannot be said whether they belong to the 'screening', 'follow-up' or 'not reimbursed' category. The coupling of these tests with IMA will be therefore authorized. If such a CHP record can be coupled to an IMA record, the CHP record is categorized according to IMA nomenclature code.

Coupling of HPV tests from CHP and IMA data

A HPV test from CHP was coupled to a HPV test from IMA database when the following conditions were fulfilled:

- Both records have the same SSN;
- The difference between the reimbursement date (date from IMA) and the incidence date (date from CHP) is ± 30 days;
- There is no nomenclature conflict: both records belong to the same category of analysis (screening/follow-up) or the nomenclature code of the CHP record is not declared, invalid or unspecific. However, if both records do not belong to the same category of analysis or if the CHP record is declared as not reimbursed, records are not coupled.

The outcome of the coupling of HPV tests from CHP and IMA database are described in Figure 68. A total of 30 652 records are coupled. If we consider that the IMA database is exhaustive for 2011 (i.e. that there is a total of 46 421 reimbursed HPV tests in 2011), this means that about 66.0% of all HPV tests in CHP are treated. This percentage is higher than the percentage of cytological samples that are treated in CHP (56.0%). This difference is due to the fact that, during the treatment of CHP records, a priority was given to the laboratories coding HPV results.

A high number of HPV records from CHP (77.6%) are not coupled to any IMA record.

The proportion of non-reimbursed HPV tests (= overconsumption) is comprised between:

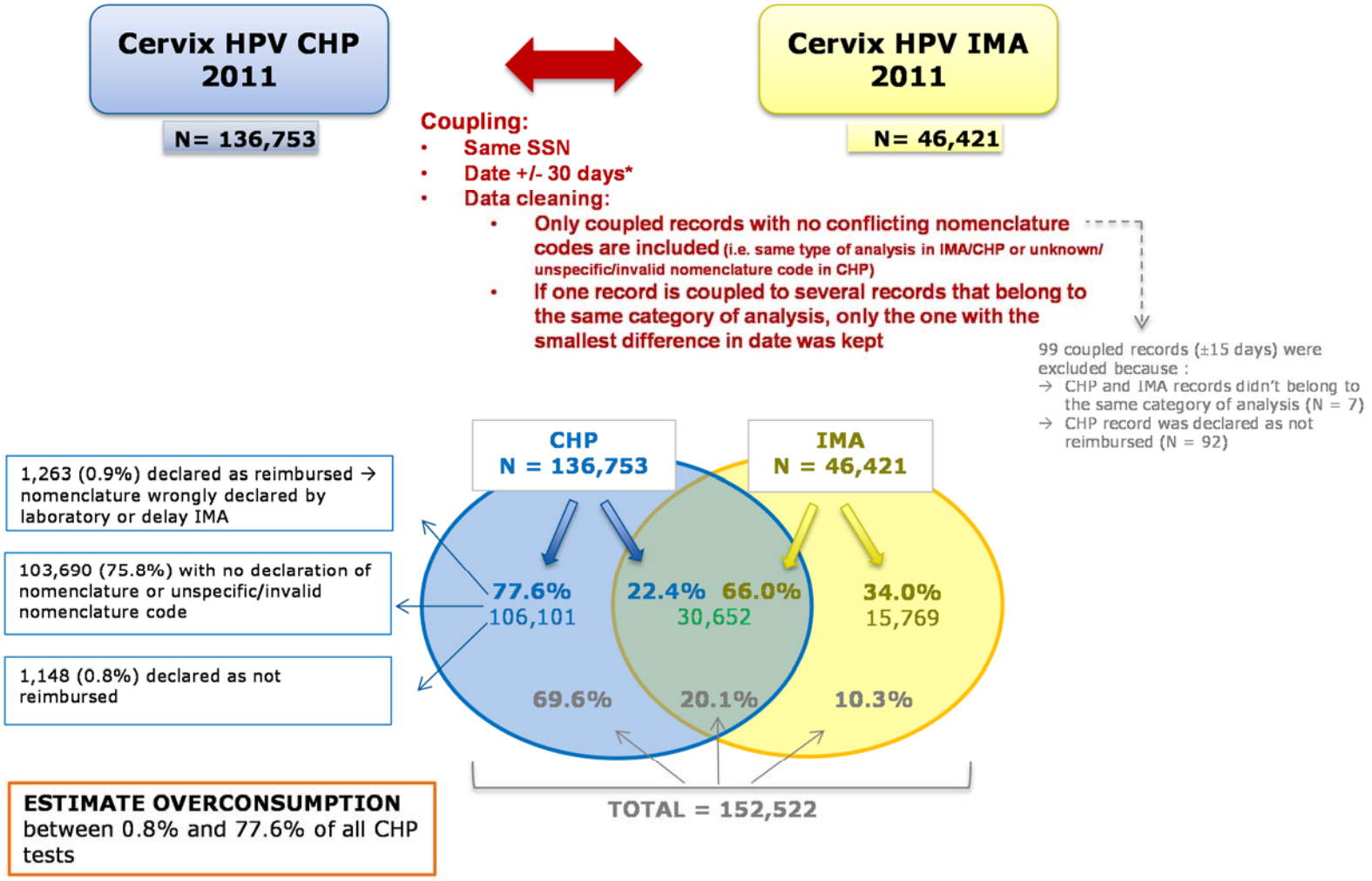
- 0.8%, which is the number of HPV tests in CHP clearly declared as not reimbursed by laboratories;
- and 77.6%, in the case where all the CHP records that are not coupled to IMA, whatever they are declared reimbursed by laboratories (0.9%) or they have an invalid nomenclature code (75.8%), are actually not reimbursed.

Note: the total number of HPV tests (reimbursed and not reimbursed) performed in 2011 is unknown:

1. the IMA data only contain reimbursed tests;
2. the CHP is not exhaustive for 2011 since only 62 of 91 laboratories are that had delivered data are included in this study;
3. the CHP contains tests for which the reimbursement status is unknown (because not declared or wrongly declared by laboratories).

However, if both the CHP and the IMA database are combined, the total number of HPV tests performed in Belgium in 2011 is estimated to 152 522 at this moment (see Figure 68).

Figure 68 – Coupling HPV tests performed in 2011 from the CHP and IMA data



* 30 days is the maximal time delay between a first reading and a HPV test. This duration was chosen as coupling criterion since the date of the HPV test in CHP often corresponds to the date of the first reading

Appendix 1.1.4.2. Analysis of CHP records with a known diagnosis/result

In this section, the analyses were performed on the CHP records for which the diagnosis/result is known. The analyses distinguish between CHP records coupled to IMA data and CHP records not coupled to IMA.

Analysis of cytological analyses with a known diagnosis

As shown in Figure 66, the diagnosis is known for 669 072 cytological analyses (557 918 cytological analyses coupled to the IMA data and 111 154 cytological analyses not coupled with IMA data).

Table 95 and Figure 69 show the distribution of diagnoses observed for cytological analyses, according to the type of analysis (first reading, second reading or follow-up).

Diagnoses were divided into the four following categories:

- Normal: no cellular anomaly
- Abnormal - benign: squamous and glandular cellular anomalies and atypical cells, including high grade squamous intraepithelial lesion (HSIL)
- Abnormal - malignant: in situ and invasive adenocarcinoma/carcinoma and other malignancies, excluding high grade squamous intraepithelial lesion (HSIL)
- No diagnosis

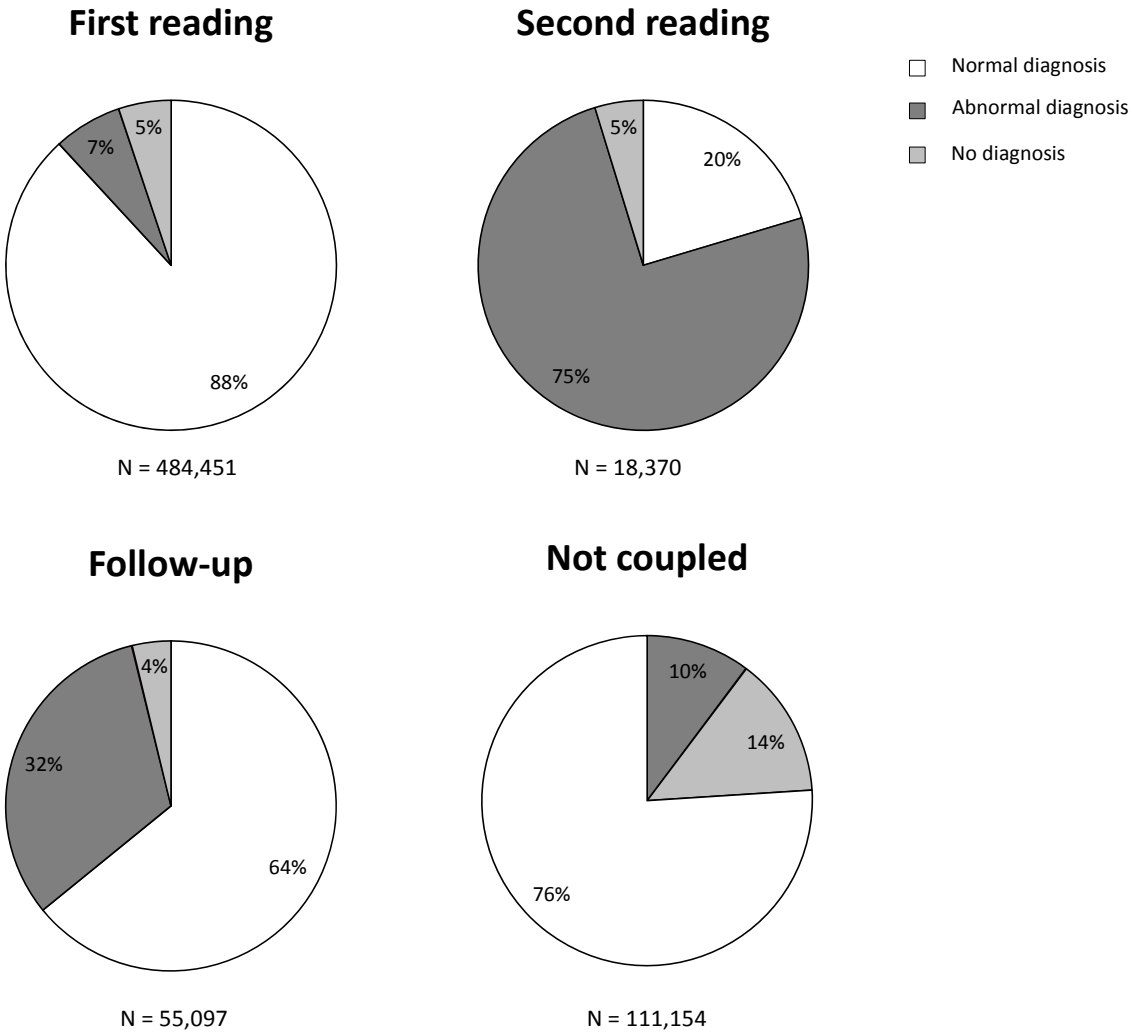
88.1% of first readings of screening tests had a normal diagnosis, while 6.7% had an abnormal diagnosis. When a second reading was performed, 74.8% of samples proved to be abnormal, while 20.4% proved to be normal. As for follow-up examinations, 64.1% and 32.0% of samples turned out normal and abnormal, respectively (Table 95 and Figure 69).

Table 95 – Distribution of diagnoses for cytological analyses performed in 2011

	Frequency nomenclature	Total	Diagnosis of cytological analyses							
			Raw numbers				Percentages			
			Normal	Abnormal – benign *	Abnormal - malignant	No diagnosis	Normal	Abnormal – benign *	Abnormal - malignant	No diagnosis
First readings of screening tests	588350-588361	484 451	427 024	32 405	164	24 858	88.1%	6.7%	0.0%	5.1%
Second readings of screening tests	588873-588884	18 370	3 740	13 732	29	869	20.4%	74.8%	0.2%	4.7%
Follow-up smears	588895-588906	55 097	35 330	17 651	41	2 075	64.1%	32.0%	0.1%	3.8%
Cytological analyses that could not be coupled to an IMA record	N/A	111 154	84 500	11 333	63	15 258	76.0%	10.2%	0.1%	13.7%
	TOTAL	**669 072**	**550 594**	**75 121**	**297**	**43 060**	**82.3%**	**11.2%**	**0.0%**	**6.4%**

(*) Including HSIL.

Figure 69 – Distribution of cytological diagnoses after first and second readings of screening tests, after follow-up smears and for samples in CHP that could not be coupled to an IMA record (year 2011)



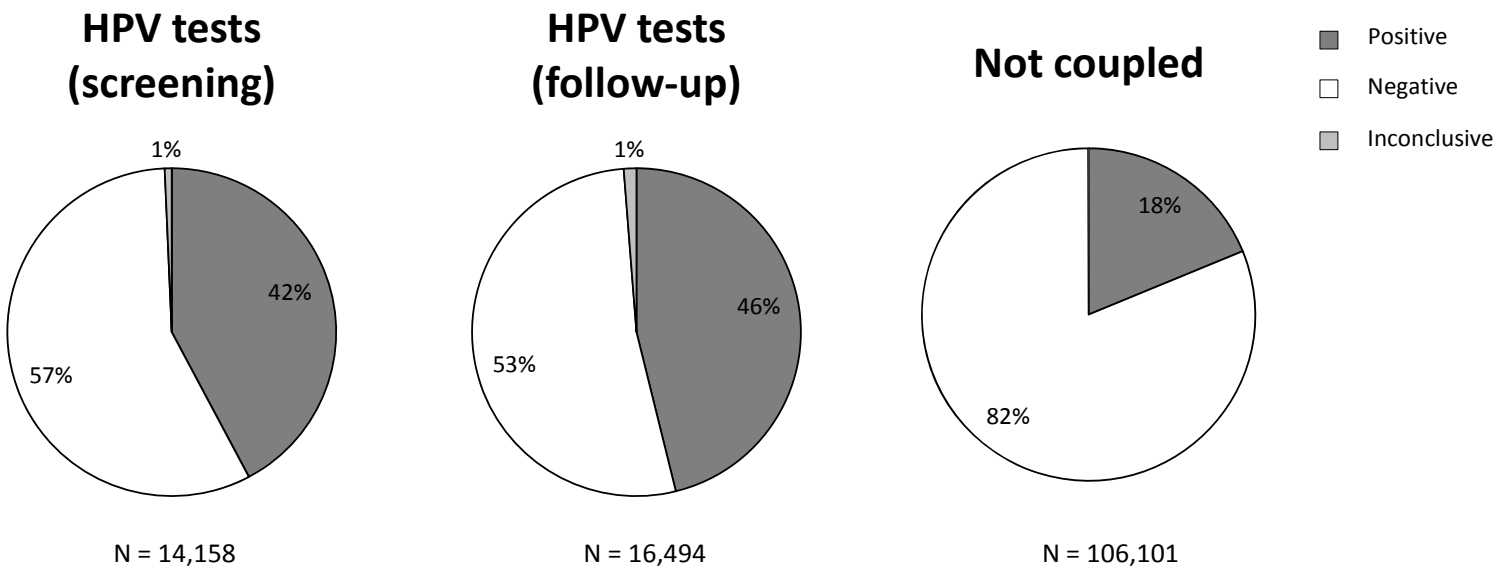
Analysis of HPV tests with a known result

As shown in Figure 14, the result of HPV tests is known for 136 753 HPV tests (30 652 HPV tests coupled to the IMA data and 106,101 HPV tests not coupled with IMA data). Table 96 and Figure 70 show the proportion of HPV tests performed as part of screening test or as part of follow-up test for the coupled CHP records. The results of HPV tests that could not be coupled to an IMA record are also shown in this table. When performed as part of screening tests, 42.2% of HPV tests were positive, while 57.1% were negative. When performed as part of follow-up examinations, 45.7% and 53.1% of HPV tests turned out positive and negative, respectively.

Table 96 – Results of HPV tests performed in 2011

	Frequency nomenclature	Total	Result of HPV tests					
			Raw numbers			Percentages		
			Positive	Negative	Inconclusive	Positive	Negative	Inconclusive
HPV tests as part of screening test	588932-588943	14 158	5 977	8 090	91	42.2%	57.1%	0.6%
HPV tests as part of follow-up examination	588954-588965	16 494	7 540	8 760	194	45.7%	53.1%	1.2%
HPV that could not be coupled to an IMA record	N/A	106 101	19 509	86 552	40	18.4%	81.6%	0.0%
	TOTAL	**136 753**	**33 026**	**103 402**	**325**	**24.2%**	**75.6%**	**0.2%**

Figure 70 – Results of HPV tests performed as part of screening or follow-up and HPV tests that could not be coupled to an IMA records (2011)



Analysis of successive further investigations that follow a screening test with a known diagnosis

In this section, the analyses were performed only on the CHP records coupled with the IMA data because the diagnosis/result (available in CHP) and the nomenclature codes (available in IMA data) were needed. It was examined whether the first readings of screening tests (CHP records coupled to IMA) were followed by a reimbursed second reading and/or HPV test, or by a reimbursed further treatment (from IMA data only).

1. Diagnoses after a first reading of a screening test

Table 97 shows that, among the first readings of screening tests for which the diagnosis is known, 95.8% were not followed by a second reading nor by a reimbursed HPV test.

Table 97 – Number of first readings of a screening test (for which the diagnosis is known) that are followed by a second reading and/or a reimbursed HPV test

	2011	
Number of first readings of screening test	484 451	100.0%
Number of first readings of screening test without second reading (<= 30 d after first reading) nor HPV test (<= 30 d after first reading)	463 967	95.8%

Figure 71 shows the difference in diagnosis distribution after first readings that are followed by a reimbursed second reading and/or a HPV test and those that are not followed by any of these investigations:

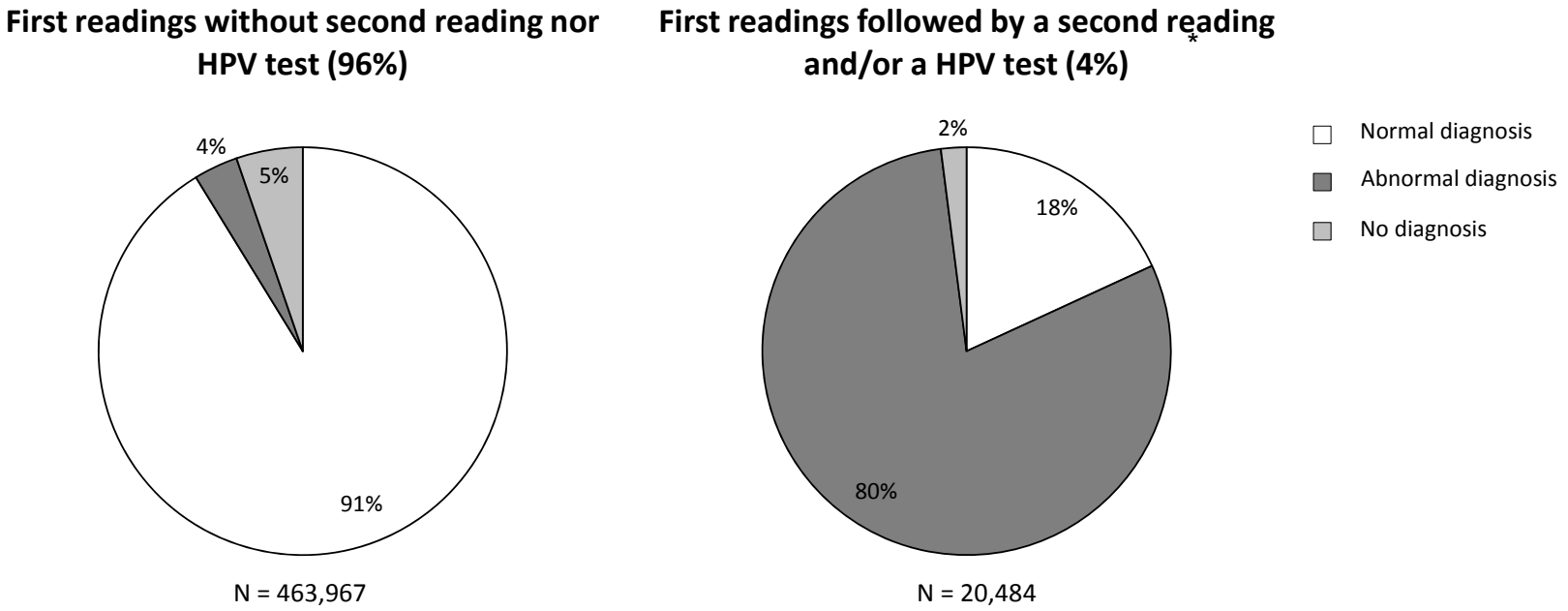
91% of first readings that were not further followed were normal, while 4% were abnormal.

80% of the first readings followed by a reimbursed second reading and/or HPV test had an abnormal diagnosis. The detail of the different cytological diagnoses is shown in the table below Figure 71.

In 18% of cases a further analysis was performed though the first reading was normal.

Note: On the total number of declared second readings in the CHP (N = 20 583), 77.4% are coded by the laboratories together with the first readings, meaning that only one result is given for both readings. Therefore, it is not known whether there was a discrepancy between the diagnosis of the first and the second reading. If this was the case, it is not known whether the delivered diagnosis is the diagnosis of the first reading or the second reading. After coupling cytological analyses from the CHP to IMA data, a total of 4776 coupled second readings were found to be coded independently of the first readings. Among those second readings preceded by a first reading (N = 2217), 69% had the same diagnosis than the first reading.

Figure 71 – Cytological diagnoses after a first reading, which is followed (right) or not (left) by a reimbursed second reading and/or HPV test (year 2011)



**Detail of cytological diagnoses after a first reading followed by a reimbursed second reading and/or HPV test*

	NORMAL	*NO DIAGNOSIS*	*ABNORMAL*	*ASCU*	*ATYP*	*ASCH*	*LSIL*	*HSIL*	*AGLC*	*SQGL*	*IN SITU*	*INVASIVE*
Raw numbers	*3714*	*413*	*16 357*	*8627*	*3630*	*618*	*1,595*	*948*	*620*	*279*	*2*	*38*
Percentages	*18.1%*	*2.0%*	*79.9%*	*42.1%*	*17.7%*	*3.0%*	*7.8%*	*4.6%*	*3.0%*	*1.4%*	*0.0%*	*0.2%*

Legend: ASCU: atypical squamous cells of undetermined significance; ATYP: atypical cells; ASCH: atypical squamous cells, cannot exclude HSIL; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; AGLC: atypical glandular cells; SQGL: combination of AGLC with either ASCU, ASCH, LSIL, or HSIL; IN SITU: IN SITU excluding HSIL.

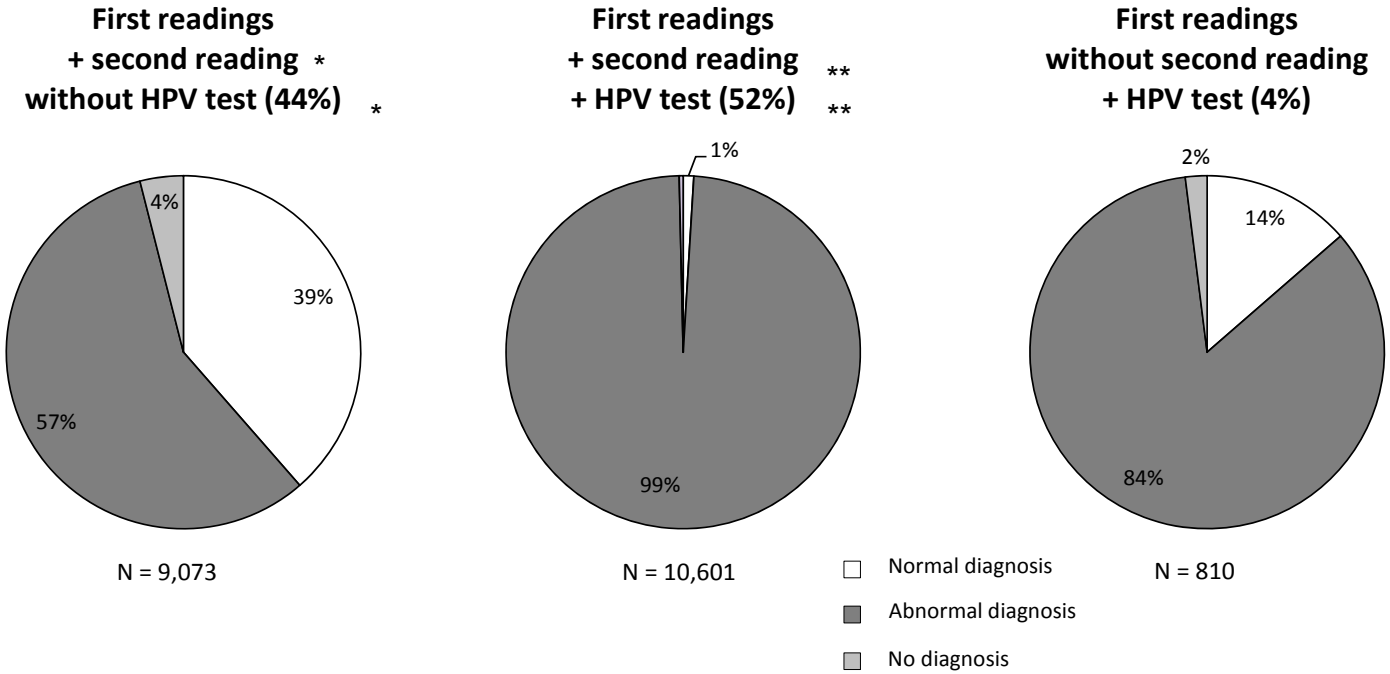
Table 98 shows the number of first readings that were followed by a second reading only, by a reimbursed HPV test only, or by both analyses.

Table 98 – Number of first readings (for which the diagnosis is known) that are followed by a second reading and/or a reimbursed HPV test (year 2011)

	2011	
Number of first readings of screening test + second reading (<= 30 d after first reading) or + HPV test as part of screening test (<= 30 d after first reading)	20 484	**100.0%**
Number of first reading of screening test **+** second reading (<= 30 d after first reading) **without** HPV test as part screening (<= 30 d after first reading)	9 073	**44.3%**
Number of first reading of screening test **without** second reading (<= 30 d after first reading) **+** HPV test as part of screening (<= 30 d after first reading)	810	**4.0%**
Number of first reading of screening test **+** second reading (<= 30 d after first reading) **+** HPV test as part of screening (<= 30 d after first reading)	10 601	**51.8%**

Figure 72 shows that 39% of the first readings followed by a second reading only were normal though 57% were abnormal. For 99% of first reading that were followed by a second reading and a reimbursed HPV test the diagnosis was abnormal.

Figure 72 – Cytological diagnoses after a first reading, which is followed by a second reading and/or a reimbursed HPV test (year 2011)



**Detail of cytological diagnoses after a first reading followed by a second reading but not by a HPV test*

	NORMAL	NO DIAGNOSIS	ABNORMAL	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	IN SITU	INVASIVE
Raw numbers	**3,502**	**359**	**5212**	1933	452	202	1,417	856	193	125	2	32
Percentages	**38.6%**	**4.0%**	**57.4%**	21.3%	5.0%	2.2%	15.6%	9.4%	2.1%	1.4%	0.0%	0.4%

***Detail of cytological diagnoses after a first reading followed by a second reading and a HPV test*

	NORMAL	NO DIAGNOSIS	ABNORMAL	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	IN SITU	INVASIVE
Raw numbers	**102**	**38**	**10 461**	6158	3124	388	157	82	402	146	0	4
Percentages	**1.0%**	**0.4%**	**98.7%**	58.1%	29.5%	3.6%	1.5%	0.8%	3.8%	1.4%	0.0%	0.0%

Legend: ASCU: atypical squamous cells of undetermined significance; ATYP: atypical cells; ASCH: atypical squamous cells, cannot exclude HSIL; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; AGLC: atypical glandular cells; SQGL: combination of AGLC with either ASCU, ASCH, LSIL, or HSIL; IN SITU: IN SITU excluding HSIL.

Histological diagnosis after surgical treatments that follow screening tests

Table 99 and Figure 73 present the nature and proportion of all further treatments performed in 2011 between 1 day and 365 days after a reimbursed screening test. The analysis distinguishes between (i) further treatments performed after a reimbursed screening test which is followed by a reimbursed second reading and HPV test, and (ii) further treatments performed after a reimbursed screening test which is followed by a second reading, but not by a reimbursed HPV test.

Table 99 – Nature and number of further surgical treatments performed in 2011 after (1-365 days) a reimbursed screening test, which is followed or not by a reimbursed HPV test

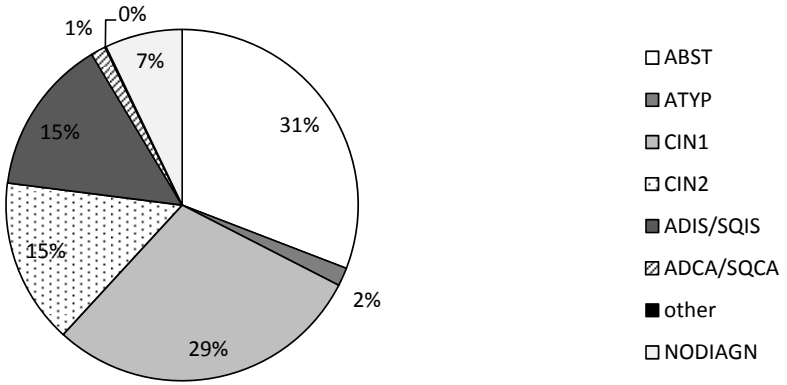
		2011	
	Nomenclature	Raw numbers	Percentages
Total number of further treatments performed after a screening test which is followed by a second reading and a HPV test:	See Appendix 1.3, Table 1	3684	100.0%
- Number of biopsy	432110-432121	2353	63.9%
- Number of conisation	432294-432305	878	23.8%
- Number of polypectomy	149052-149063	60	1.6%
- Number of hysterectomy	431270-431281 431314-431325 431336-431340 431351-431362 432670-432681 432736-432740	259	7.0%
- Number of amputation	431491-431502	132	3.6%
- Other		2	0.0%
Total number of further treatments performed after a screening test which is followed by a second reading but not by a HPV test:	See Appendix 1.3, Table 1	3074	100.0%
- Number of biopsy	432110-432121	1769	57.6%
- Number of conisation	432294-432305	925	30.1%
- Number of polypectomy	149052-149063	31	1.0%
- Number of hysterectomy	431270-431281 431314-431325 431336-431340 431351-431362 432670-432681 432736-432740	213	6.9%
- Number of amputation	431491-431502	133	4.3%
- Other		3	0.1%

Note: the analysis takes into account all further treatments performed after screening tests, without distinguishing possible combinations performed after a same screening test.

Further surgical treatments that were performed in 2011 after a reimbursed screening test have been coupled (± 15 days) to histological analyses from the CHP database. Figure 19 below shows the diagnosis registered after those coupled surgical treatments.

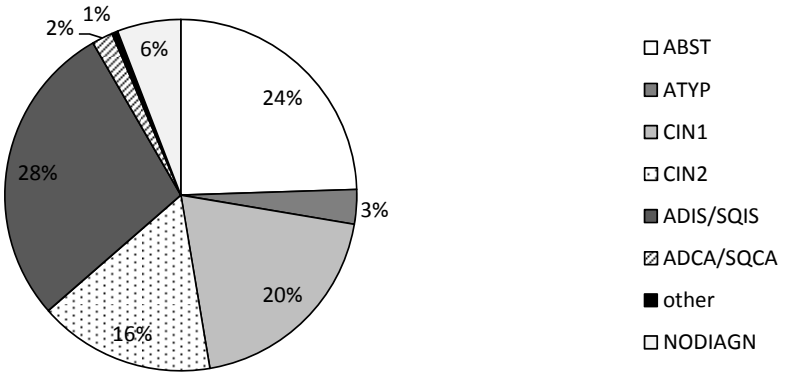
Figure 73 – Histological diagnoses after further surgical treatments performed in 2011 after (1-365 days) a screening test, which is followed (left) or not (right) by a reimbursed HPV test

Results of treatments performed in 2011 after a screening test which is followed by second reading **and a HPV test**



N = 2,132

Results of treatments performed in 2011 after a screening test which is followed by second reading **but not by a HPV test**

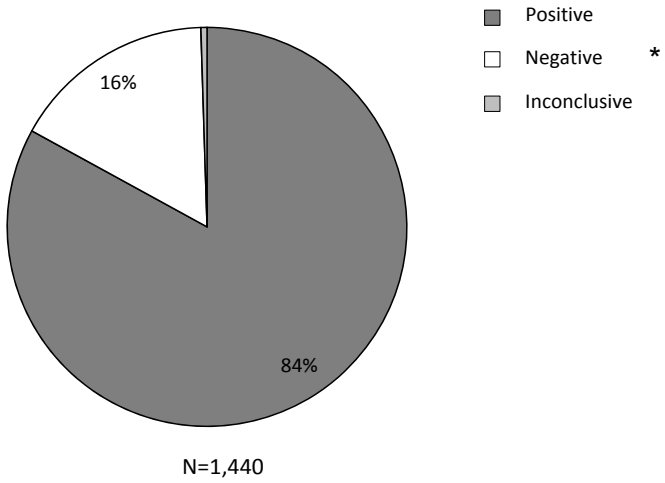


N = 1,609

Legend: ABST: no dysplasia, no tumor; ATYP: atypical cells; CIN1: mild dysplasia; CIN2: moderate dysplasia; ADIS/SQIS: adenocarcinoma and squamous carcinoma in situ; ADCA/SQCA: adenocarcinoma and squamous carcinoma; NODIAGN: no diagnosis

Among the further treatments that are preceded by a second reading and a HPV test, 1,440 could have been coupled in CHP to the corresponding HPV result. Figure 74 shows that 84% of known HPV tests that preceded a further treatment in 2011 were positive, though 16% were negative. Please note that only HPV tests present in the CHP were taken into consideration for those analyses (since the results of HPV tests present in IMA data only are not known). Consequently those results represent a sub-selection of the total population. These 237 negative HPV screening tests that are followed by a further treatment, were investigated more in details (Figure 74). More particularly, the cytological diagnosis of the original screening test and the nature of further treatments after the screening test are shown. The histological diagnoses after the further treatment (as far as available in CHP) are also shown in Figure 74. Only a limited number of histological diagnoses can be found (77 of the 237), probably due to a relative high percentage of glandular abnormalities (46 AGLC on the total of 237 cytological diagnoses and 64 hysterectomies on the total of 237 treatments). The CHP only contains cervical samples. For those 237 women, the occurrence of a medical act of the category ‘extra’ was also investigated.

Figure 74 – Results of HPV tests performed after a reimbursed screening test which is followed by a further treatment in 2011



N=1,440

Details on the cytological diagnoses of the reimbursed screening tests which were followed by a negative HPV test and by a further treatment:

Diagnosis	*NILM*	*NODIAGN*	*ASCU*	*ATYP*	*LSIL*	*HSIL*	*AGLC*	*ASCH*	*SQGL*	*Unknown (not coupled to CHP)*	*Total*
Number	*4*	*19*	*85*	*22*	*3*	*4*	*46*	*32*	*5*	*17*	*237*

NILM: negative for intraepithelial lesion of malignancy; NODIAGN: no diagnosis; ASCU: atypical squamous cells of undetermined significance; ATYP: atypical cells; ASCH: atypical squamous cells, cannot exclude HSIL; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; AGLC: atypical glandular cells; SQGL: combination of AGLC with either ASCU, ASCH, LSIL, or HSIL.

Details on the treatments performed after the reimbursed screening tests which were followed by a negative HPV test:

Treatment	*Polypectomy*	*Hysterectomy*	*Amputation*	*Biopsy*	*Conisation*	*Total*
Number	*10*	*64*	*3*	*143*	*17*	*237*

Details on the histological diagnoses after the treatments that were performed after a reimbursed screening test followed by a negative HPV test:

Diagnosis	*ABST*	*ATYP*	*CIN1*	*CIN2*	*SQIS*	*SQCA*	*ADCA*	*ADSQCA*	*META*	*NODIAGN*	*Unknown (not coupled to CHP)*	*Total*
Number	*88*	*5*	*38*	*5*	*1*	*1*	*1*	*1*	*1*	*19*	*77*	*237*

ABST: no dysplasia; ATYP: atypical cells; CIN1: mild dysplasia; CIN2: moderate dysplasia; SQIS: squamous carcinoma in situ; ADCA/ADSQCA: adenocarcinoma (and squamous carcinoma); NODIAGN: no diagnosis

Details on extra treatments performed after (1-365d) the reimbursed screening tests which were followed by a negative HPV test and a further treatment:

Treatment	*Cervical curettage*	*Diagnostical hysteroscopy*	*No extra treatment*	*Total*
Number	*26*	*21*	*190*	*237*

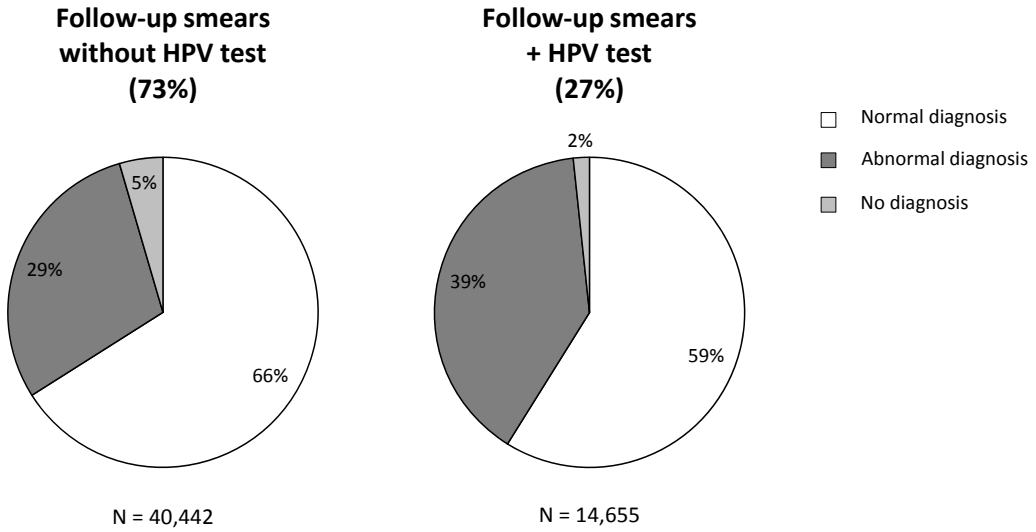
Diagnoses after a follow-up test

Table 100 shows that, among the follow-up smears for which the diagnosis is known, 26.6% were followed by a reimbursed HPV test. Figure 75 shows the distribution of diagnoses after cervix smears performed as part of follow-up examinations.

Table 100 – Number of follow-up smears (for which diagnosis is known) followed or not by a reimbursed HPV test (year 2011)

	2011	
Number of follow-up smears	55 097	100.0%
Number of follow-up smears without HPV test as part of follow-up examination (<= 30 d after follow-up smear)	40 442	73.4%
Number of follow-up smears with HPV test as part of follow-up examination (<= 30 d after follow-up smear)	14 655	26.6%

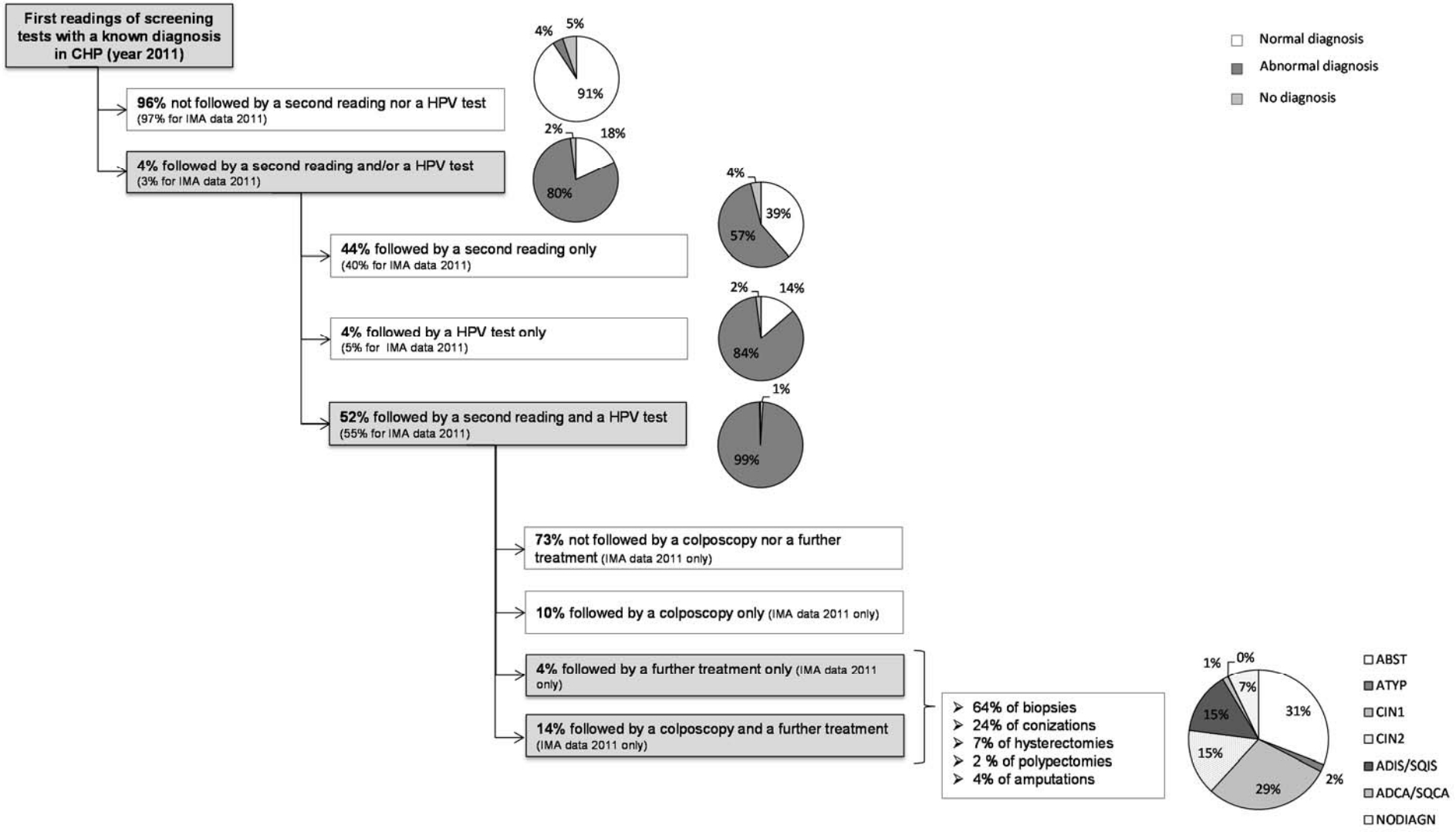
Figure 75 – Cytological diagnoses after follow-up smears, which are followed or not by a reimbursed HPV test (year 2011)



Summary

Figure 76 summarizes the main results obtained from these analyses.

Figure 76 – Summary



Appendix 1.1.5. Detailed analysis of cervix CHP results

In this part of the report, the results of the cervix CHP are analyzed in more details. The results are analyzed in correlation with the results of HPV tests and results are shown at the level of individual laboratories that performed the analyses. On the total of 91 laboratories, data from 62 laboratories were processed and analyzed. These 62 laboratories were selected based on the quality of the data provided, especially on the percentage of reported HPV test results.

Note: the analyses for this fifth part were done after those performed in parts 1 to 4. Since the CHP is a dynamic database, some slight differences exist in the results between this part and parts 1 to 4.

Appendix 1.1.5.1. Correlation cytology-virology

In this paragraph the cytological diagnoses of the smears in the CHP were correlated with the results of the HPV test performed (year 2011).

General cytological and HPV results

In a first step the global frequency of the different cytological diagnoses in the CHP were analyzed. The cytological diagnoses are subdivided by the type of the medical act. The type of the medical act was determined after coupling the cervix CHP smears of 2011 with the IMA database. The coupling and data cleaning procedure used, is described in point 4.1.1. Based on the coupled nomenclature codes, the reimbursed samples are subdivided into first readings of screening tests (588350, 558361), second readings of screening tests (588873, 588884) and follow-up tests (588895, 588906). Smears that could not be coupled to an IMA record were considered as not reimbursed samples. The meaning of the different cytological diagnoses are listed in Table 101.

Table 101 – Definition of the different cytological diagnoses

Cytological diagnosis	Meaning	
NILM	Negative for intraepithelial lesion of malignancy	Negative for intraepithelial lesion of malignancy
ASCU	Atypical squamous cells of undetermined significance	Epithelial cell abnormalities - squamous
ATYP	Atypical cells, not otherwise specified	Epithelial cell abnormalities - not specified
ASCH	Atypical squamous cells, cannot exclude HSIL	Epithelial cell abnormalities - squamous
LSIL	Low-grade squamous intraepithelial lesion	Epithelial cell abnormalities - squamous
HSIL	High-grade squamous intraepithelial lesion	Epithelial cell abnormalities - squamous
AGLC	Atypical glandular cells	Epithelial cell abnormalities - glandular
SQGL	Combination of AGLC with either ASCU, ASCH, LSIL or HSIL	Epithelial cell abnormalities - squamous & glandular
IN SITU	Adenocarcinoma, adenosquamous carcinoma (in situ), exclusion of HSIL	Epithelial cell carcinoma in situ
INVASIVE	Squamous carcinoma, adenocarcinoma, adenosquamous carcinoma (invasive)	Epithelial cell carcinoma invasive
OTHER	In situ or invasive tumors, except squamous carcinoma, adenocarcinoma, adenosquamous carcinoma Metastases in the cervix or tumor invasion of the cervix	All other malignancies (in situ of invasive)
NODIAGN	No diagnosis	-

Table 102 shows the overall frequency and the relative percentage of the diagnoses of all cytological analyses that are present in the cervix CHP for the year 2011.

Table 102 – Frequency and percentage of cytological diagnoses in the treated CHP per type of medical act (year 2011)

Type of medical act	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	IN SITU*	INVASIVE	OTHER	NODIAGN	TOTAL
Raw numbers													
First reading	427 067	10 501	9 865	771	7 708	1 842	1 405	321	4	110	50	24 863	484 507
Second reading	3 741	6 552	3 499	584	1 417	900	526	253	4	16	9	869	18 370
Follow-up	35 335	4 693	3 099	497	7 449	1 560	235	117	2	20	19	2 076	55 102
Not coupled to IMA record	84 590	4 324	2 736	375	2 668	775	352	125	4	43	16	15 304	111 312
TOTAL	550 733	26 070	19 199	2 227	19 242	5 077	2 518	816	14	189	94	43 112	669 291
Percentages													
First reading	88.1%	2.2%	2.0%	0.2%	1.6%	0.4%	0.3%	0.1%	0.0%	0.0%	0.0%	5.1%	100.0%
Second reading	20.4%	35.7%	19.0%	3.2%	7.7%	4.9%	2.9%	1.4%	0.0%	0.1%	0.0%	4.7%	100.0%
Follow-up	64.1%	8.5%	5.6%	0.9%	13.5%	2.8%	0.4%	0.2%	0.0%	0.0%	0.0%	3.8%	100.0%
Not coupled to IMA record	76.0%	3.9%	2.5%	0.3%	2.4%	0.7%	0.3%	0.1%	0.0%	0.0%	0.0%	13.7%	100.0%
TOTAL	82.3%	3.9%	2.9%	0.3%	2.9%	0.8%	0.4%	0.1%	0.0%	0.0%	0.0%	6.4%	100.0%

** Exclusive HSIL.*

Figure 77 shows the overall frequency of the diagnoses of all cytological samples present in the cervix CHP.

Figure 77 – Frequency of cytological diagnoses in the CHP per type of medical act (year 2011)

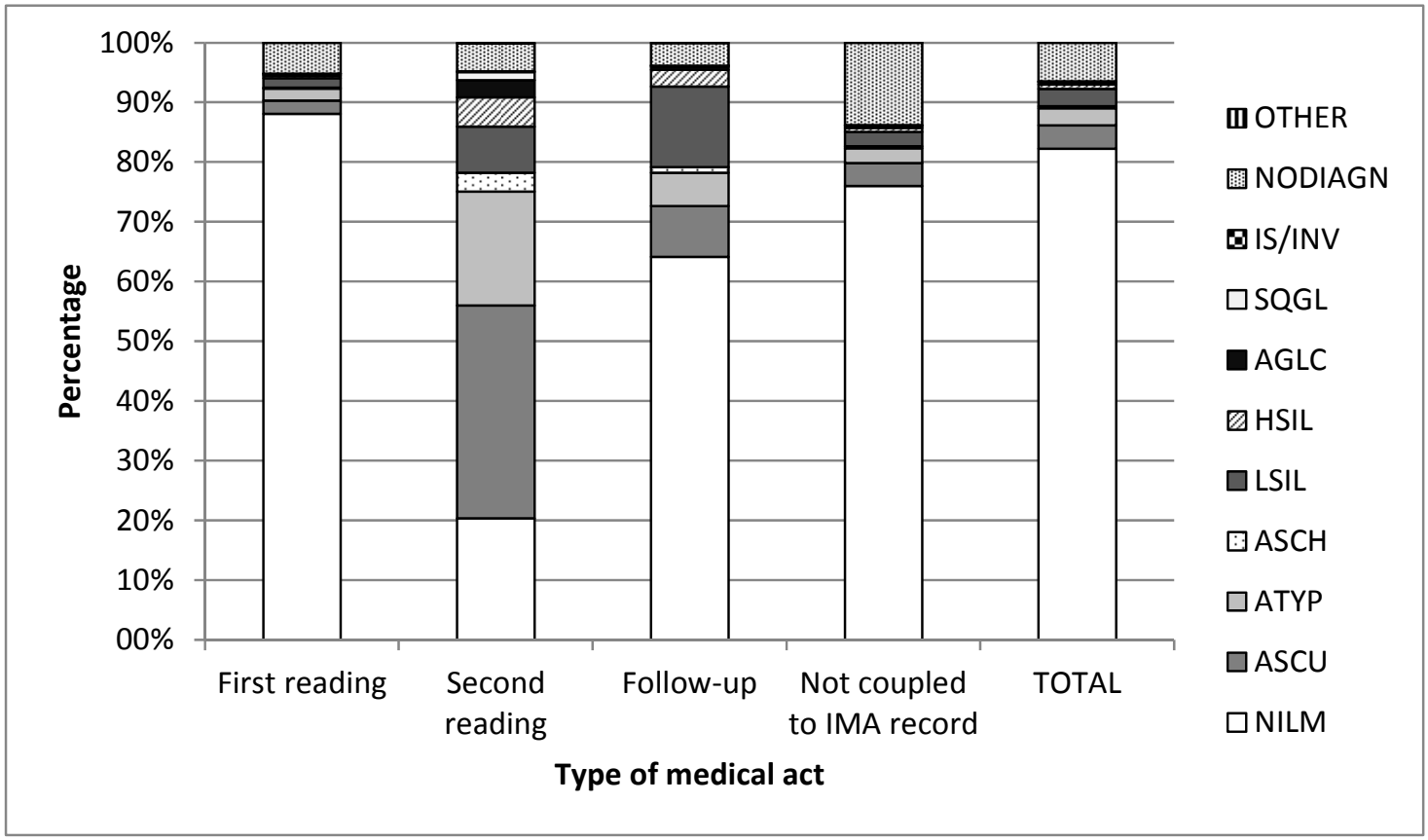


Table 103 shows the overall frequency and the relative percentage of the diagnoses and the HPV test results of all cytological samples that are present in the cervix CHP for the year 2011.

Table 103 – Frequency and percentage of cytological diagnoses (in CHP) and following HPV test results (≤ 30 days; in CHP and IMA) per type of medical act (year 2011)

HPV result		Type of medical act							
		Raw numbers				Percentages			
		First reading	Follow-up	Not coupled to IMA record	TOTAL	First reading	Follow-up	Not coupled to IMA record	TOTAL
NILM	**HPV+**	6 082	5 146	1 452	12 680	1.42%	14.56%	1.72%	2.32%
	HPV-	65 356	10 226	11 922	87 504	15.30%	28.94%	14.14%	16.01%
	HPVi	5	56	2	63	0.00%	0.16%	0.00%	0.01%
	HPV result unknown	78	405	142	625	0.02%	1.15%	0.17%	0.11%
	No HPV	355 546	19 502	70 797	445 845	83.25%	55.19%	83.97%	81.55%
	Total	427 067	35 335	84 315	546 717	100.00%	100.00%	100.00%	100.00%
ASCU	**HPV+**	2 528	1 346	647	4 521	24.07%	28.68%	16.90%	23.77%
	HPV-	4 887	1 480	914	7 281	46.54%	31.54%	23.88%	38.28%
	HPVi	64	21	1	86	0.61%	0.45%	0.03%	0.45%
	HPV result unknown	511	285	172	968	4.87%	6.07%	4.49%	5.09%
	No HPV	2 511	1 561	2 094	6 166	23.91%	33.26%	54.70%	32.42%
	Total	10 501	4 693	3 828	19 022	100.00%	100.00%	100.00%	100.00%
ATYP	**HPV+**	2 054	1 862	548	4 464	20.82%	60.08%	22.42%	28.97%
	HPV-	1 137	385	308	1 830	11.53%	12.42%	12.60%	11.88%
	HPVi	2	20	1	23	0.02%	0.65%	0.04%	0.15%
	HPV result unknown	313	117	33	463	3.17%	3.78%	1.35%	3.00%
	No HPV	6 359	715	1 554	8 628	64.46%	23.07%	63.58%	56.00%
	Total	9 865	3 099	2 444	15 408	100.00%	100.00%	100.00%	100.00%
ASCH	**HPV+**	288	168	91	547	37.35%	33.80%	27.83%	34.29%
	HPV-	237	78	57	372	30.74%	15.69%	17.43%	23.32%
	HPVi	9	4	1	14	1.17%	0.80%	0.31%	0.88%
	HPV result unknown	23	99	15	137	2.98%	19.92%	4.59%	8.59%
	No HPV	214	148	163	525	27.76%	29.78%	49.85%	32.92%
	Total	771	497	327	1 595	100.00%	100.00%	100.00%	100.00%
LSIL	**HPV+**	2 376	3 102	621	6 099	30.83%	41.64%	24.31%	34.43%
	HPV-	355	284	112	751	4.61%	3.81%	4.38%	4.24%
	HPVi	2	14	2	18	0.03%	0.19%	0.08%	0.10%
	HPV result unknown	29	30	13	72	0.38%	0.40%	0.51%	0.41%
	No HPV	4 946	4 019	1 807	10 772	64.17%	53.95%	70.72%	60.82%
	Total	7 708	7 449	2 555	17 712	100.00%	100.00%	100.00%	100.00%
HSIL	**HPV+**	472	521	129	1 122	25.62%	33.40%	18.25%	27.31%

	HPV-	36	21	5	62	1.95%	1.35%	0.71%	1.51%
	HPVi	0	2	0	2	0.00%	0.13%	0.00%	0.05%
	HPV result unknown	14	21	32	67	0.76%	1.35%	4.53%	1.63%
	No HPV	1 320	995	541	2 856	71.66%	63.78%	76.52%	69.51%
	Total	1 842	1 560	707	4 109	100.00%	100.00%	100.00%	100.00%
AGLC	**HPV+**	80	66	37	183	5.69%	28.09%	11.49%	9.33%
	HPV-	410	77	54	541	29.18%	32.77%	16.77%	27.57%
	HPVi	4	3	0	7	0.28%	1.28%	0.00%	0.36%
	HPV result unknown	23	5	5	33	1.64%	2.13%	1.55%	1.68%
	No HPV	888	84	226	1 198	63.20%	35.74%	70.19%	61.06%
	Total	1 405	235	322	1 962	100.00%	100.00%	100.00%	100.00%
SQGL	**HPV+**	71	35	19	125	22.12%	29.91%	20.43%	23.54%
	HPV-	106	27	14	147	33.02%	23.08%	15.05%	27.68%
	HPVi	0	0	0	0	0.00%	0.00%	0.00%	0.00%
	HPV result unknown	98	1	12	111	30.53%	0.85%	12.90%	20.90%
	No HPV	46	54	48	148	14.33%	46.15%	51.61%	27.87%
	Total	321	117	93	531	100.00%	100.00%	100.00%	100.00%
IN SITU*	**HPV+**	0	0	0	0	0.00%	0.00%	0.00%	0.00%
	HPV-	0	0	0	0	0.00%	0.00%	0.00%	0.00%
	HPVi	0	0	0	0	0.00%	0.00%	0.00%	0.00%
	HPV result unknown	0	0	0	0	0.00%	0.00%	0.00%	0.00%
	No HPV	4	2	4	10	100.00%	100.00%	100.00%	100.00%
	Total	4	2	4	10	100.00%	100.00%	100.00%	100.00%
INVASIVE	**HPV+**	6	5	1	12	3.75%	12.82%	1.79%	4.71%
	HPV-	2	1	0	3	1.25%	2.56%	0.00%	1.18%
	HPVi	0	0	0	0	0.00%	0.00%	0.00%	0.00%
	HPV result unknown	3	1	0	4	1.88%	2.56%	0.00%	1.57%
	No HPV	149	32	55	236	93.13%	82.05%	98.21%	92.55%
	Total	160	39	56	255	100.00%	100.00%	100.00%	100.00%
NODIAGN	**HPV+**	35	111	2 457	2 603	0.14%	5.35%	16.08%	6.17%
	HPV-	138	206	3 851	4 195	0.56%	9.92%	25.20%	9.94%
	HPVi	2	3	105	110	0.01%	0.14%	0.69%	0.26%
	HPV result unknown	6	72	95	173	0.02%	3.47%	0.62%	0.41%
	No HPV	24 682	1 684	8 775	35 141	99.27%	81.12%	57.42%	83.23%
	Total	24 863	2 076	15 283	42 222	100.00%	100.00%	100.00%	100.00%
TOTAL	**HPV+**	13 992	12 362	6 002	32 356	2.89%	22.43%	5.46%	4.98%
	HPV-	72 664	12 785	17 237	102 686	15.00%	23.20%	15.68%	15.81%
	HPVi	88	123	112	323	0.02%	0.22%	0.10%	0.05%
	HPV result unknown	1 098	1 036	519	2 653	0.23%	1.88%	0.47%	0.41%

No HPV	396 665	28 796	86 064	511 525	81.87%	52.26%	78.29%	78.75%
Total	484 507	55 102	109 934	649 543	100.00%	100.00%	100.00%	100.00%

**Exclusive HSIL*
(†) HPV+, HPV-, HPVi = HPV test present in CHP only or in CHP and IMA (result is consequently known); HPV result unknown = HPV test present in IMA only (result is consequently unknown); no HPV = no HPV test registered in CHP or IMA

The frequencies of the different HPV genotypes that are registered in the cervix CHP for HPV tests performed in 2011 as part of screening tests are represented in Table 104. The occurrence of each subtype is shown per cytological diagnosis of the corresponding sample. HPV genotypes that are considered to be high risk are indicated in dark gray. Genotypes considered as probably high risk or undetermined high risk are indicated in light gray. HPV 53 is considered as a genotyped with undetermined high risk, HPV 66 as a genotype with probably high risk. The categorization of the HPV types regarding the risk level was based on information provided by Dr. Marc Arbyn (personal communication of 19/11/2012).

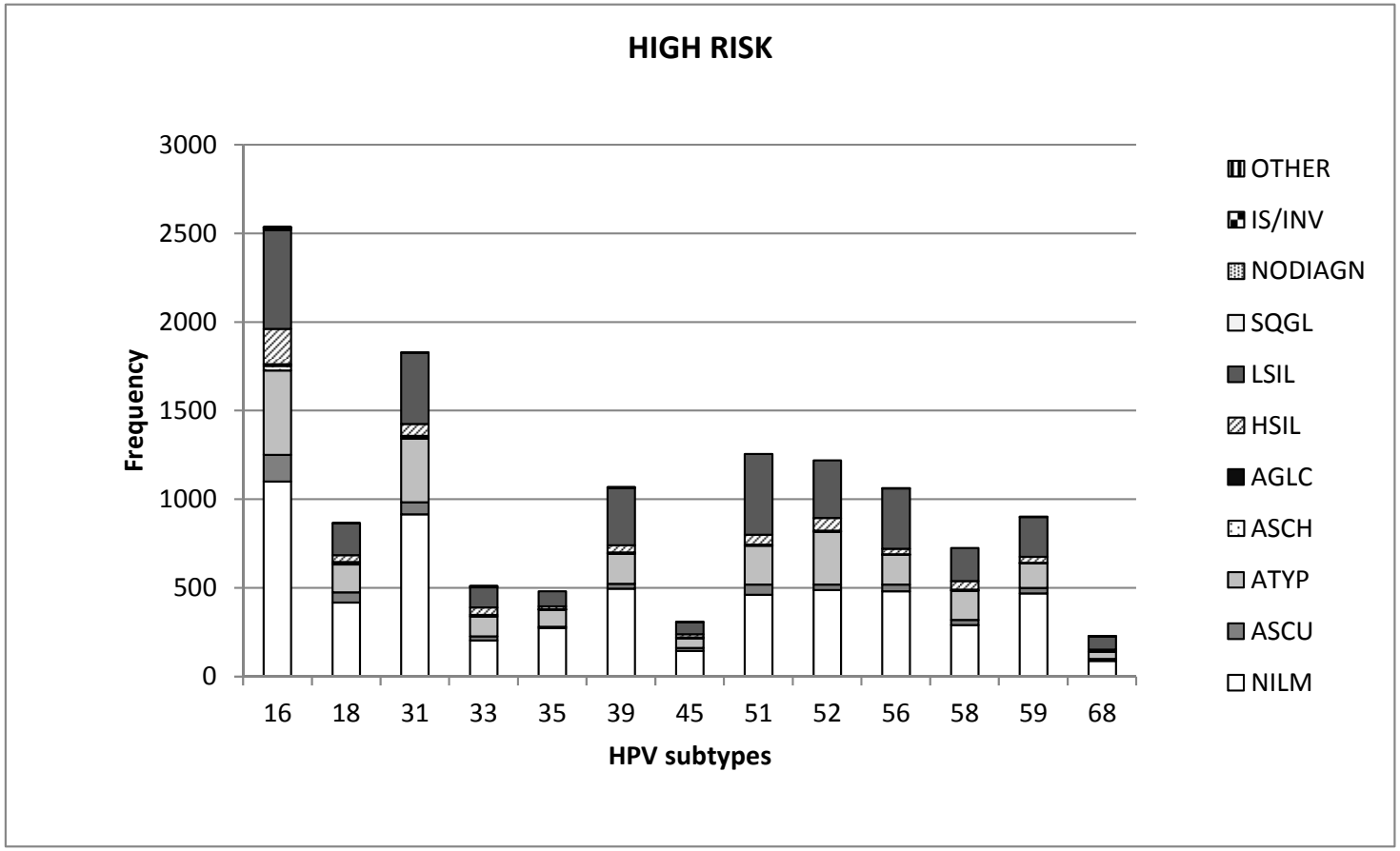
Table 104 – Frequency of HPV subtypes per cytological diagnosis (after first readings only) in the CHP (year 2011)

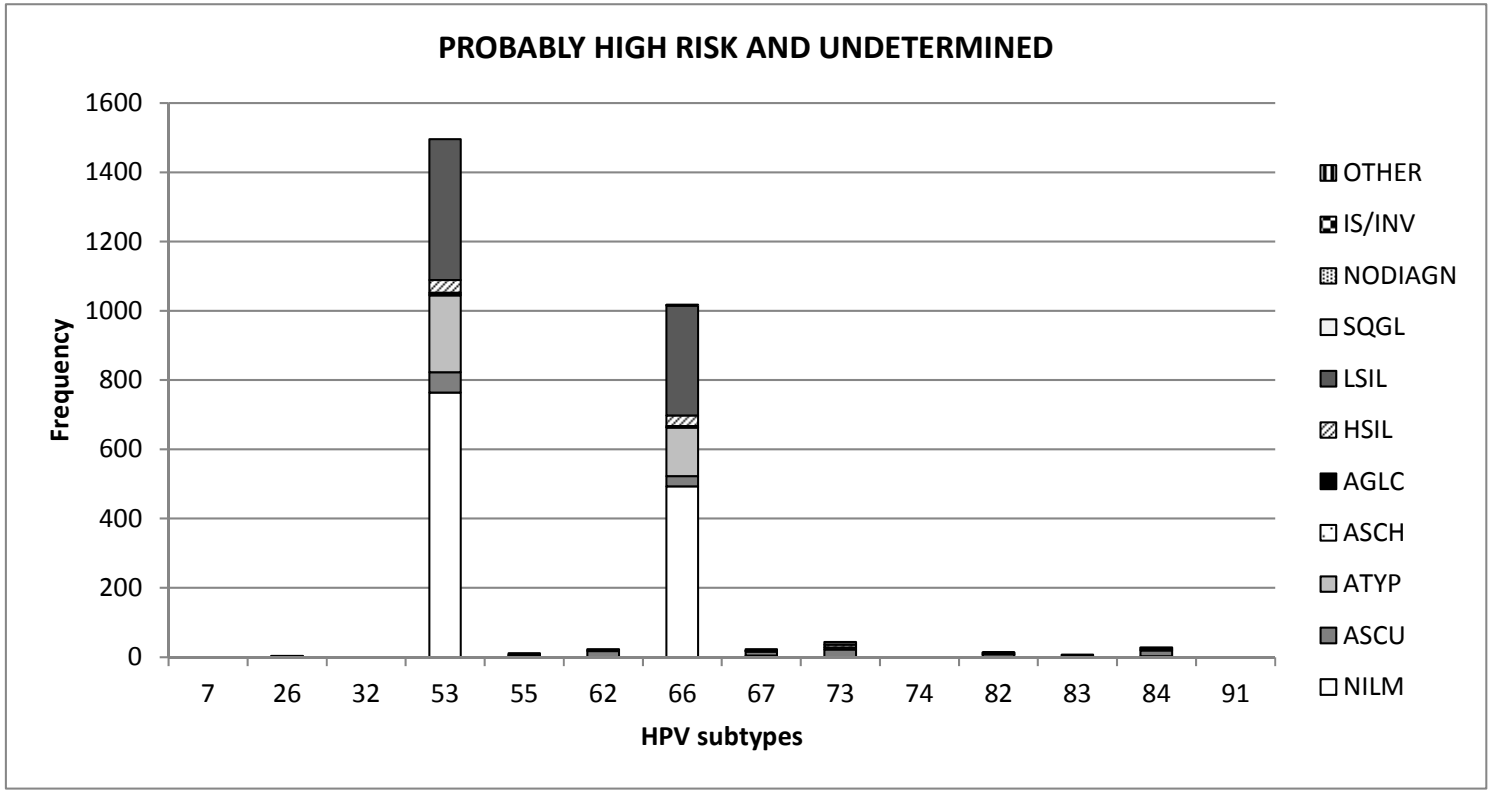
	Cytological diagnosis											
HPV subtype	NILM	ASCU	ATYP	ASCH	AGLC	HSIL	LSIL	SQGL	NODIAGN	IS/INV	OTHER	Total
1	0	0	7	0	0	0	0	0	0	0	0	7
5	0	0	1	0	0	0	0	0	0	0	0	1
6	200	11	100	0	1	8	110	0	0	0	0	430
7	0	0	1	0	0	0	0	0	0	0	0	1
8	0	0	1	0	0	0	0	0	0	0	0	1
11	52	3	22	2	1	2	37	0	0	0	0	119
13	0	0	1	0	0	0	0	0	0	0	0	1
16	1098	150	478	24	11	200	558	10	2	3	1	2535
18	415	58	157	6	7	40	178	4	0	0	0	865
26	1	2	0	0	0	1	0	0	0	0	0	4
31	914	66	360	12	4	68	401	1	0	0	0	1826
32	0	0	1	0	0	0	0	0	0	0	0	1
33	200	24	111	10	0	42	115	4	3	0	0	509
35	270	7	98	1	1	17	85	0	0	0	0	479
39	493	27	170	3	4	40	325	3	1	0	0	1066
40	0	3	1	0	0	0	1	0	0	0	0	5
42	1	28	1	3	0	3	8	0	0	0	0	44
44	0	0	1	0	0	0	0	0	0	0	0	1
45	142	16	55	6	0	16	70	1	0	0	0	306
51	459	57	220	2	3	57	456	0	0	0	0	1254
52	485	31	299	1	4	72	325	0	0	0	0	1217
53	764	59	222	4	4	36	407	0	0	0	0	1496
54	0	18	0	0	0	3	2	0	0	0	0	23
55	0	4	1	2	0	2	3	0	0	0	0	12
56	478	39	168	1	1	32	340	0	1	0	0	1060
58	288	28	166	2	3	49	187	0	0	0	0	723
59	466	32	137	2	2	34	224	1	0	0	0	898
61	0	8	0	3	0	1	2	1	0	0	0	15
62	2	16	0	0	0	3	3	0	0	0	0	24
66	493	30	141	1	3	30	317	2	1	0	0	1018
67	5	12	0	1	1	1	4	0	0	0	0	24
68	86	11	40	1	1	10	74	0	1	0	1	225
70	1	4	1	1	0	3	2	0	0	0	0	12
72	0	1	0	0	0	0	0	0	1	0	0	2
73	0	23	0	5	0	8	8	0	0	0	0	44
74	0	0	1	0	0	0	0	0	0	0	0	1
81	0	7	0	1	0	1	0	0	0	0	0	9
82	0	9	0	1	0	3	2	0	0	0	0	15
83	1	5	0	0	0	0	2	0	0	0	0	8

84	3	17	0	0	0	3	4	1	0	0	0	28
89	0	22	0	1	0	1	5	0	0	0	0	29
91	0	0	1	0	0	0	0	0	0	0	0	1
L1	1257	0	551	0	6	134	702	0	0	0	0	2650

The frequencies of high, probably high and undetermined high risk HPV subtypes and in the treated CHP are represented in Figure 78.

Figure 78 – Frequency of high, probably high and undetermined high risk HPV subtypes per cytological analyses (first readings only) in the CHP (year 2011)





Remark: HPV 53: undetermined high risk, HPV 66: probably high risk

Cytological results per laboratory

The total number of cytological analyses (first readings only) registered in the CHP for 2011 per laboratory are summarized in Table 105 and Table 106. The frequency and distribution of the different cytological diagnoses are shown as raw numbers in Table 105 and as percentages in Table 106. The second to last column of Table 106 mentions which method is used to analyze the smears in 2011 (conventional of liquid based). In the last column of Table 38 is indicated whether or not the diagnosing is automated by an imaging system. If this is the case, the system used is mentioned.

Table 105 – Frequency of cytological diagnoses (after first readings only) in the CHP per laboratory (raw data, year 2011)

Lab	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN
Lab 1	2 162	1 978	55	11	-	47	5	3	-	-	-	-	-	-	-	-	63
Lab 2	7 004	6 731	30	2	-	164	33	8	2	-	-	-	-	-	1	-	33
Lab 3	2 191	2 152	7	2	1	16	9	2	-	-	-	-	-	-	-	-	2
Lab 4	401	363	11	-	25	-	1	-	-	-	-	-	-	-	-	-	1
Lab 5	8 945	8 625	80	5	5	175	33	1	-	-	-	-	2	-	1	1	17
Lab 6	1 214	1 142	22	3	4	18	3	4	-	-	-	-	-	1	1	-	16
Lab 7	8 093	7 336	443	57	-	160	29	14	25	-	-	-	-	-	2	-	27
Lab 8	5 208	4 681	-	-	99	2	2	-	-	-	-	-	1	-	-	-	423
Lab 9	6 794	6 012	3	-	105	62	19	6	1	-	-	-	-	-	1	-	585
Lab 10	9 489	8 941	-	-	369	86	58	4	1	1	-	-	-	-	-	-	29
Lab 11	957	875	63	2	-	4	2	2	6	-	-	-	-	-	-	-	3
Lab 12	684	626	16	1	25	7	2	7	-	-	-	-	-	-	-	-	-
Lab 13	2 587	2 421	126	1	1	11	5	3	3	-	-	-	-	-	-	1	15
Lab 14	3 282	3 155	22	1	1	67	23	1	1	-	-	-	2	-	1	-	8
Lab 15	76 291	70 968	-	-	2 423	2 374	347	151	1	-	-	-	-	1	-	-	26
Lab 16	16 729	15 587	341	17	2	344	68	18	-	-	-	-	4	4	1	1	342
Lab 17	4 667	4 457	54	1	137	4	5	9	-	-	-	-	-	-	-	-	-
Lab 18	15 164	14 369	360	27	4	143	62	12	-	-	-	-	-	1	-	-	186
Lab 19	11 480	10 481	456	13	-	421	59	4	2	-	-	-	2	-	-	-	42
Lab 20	11 437	30	356	1	8	220	39	4	3	-	-	-	2	-	3	-	10 771
Lab 21	14 409	7 387	128	41	580	6	5	200	2	-	-	-	2	1	-	12	6 045
Lab 22	10 533	10 171	63	25	-	62	26	5	-	-	-	-	-	-	-	-	181
Lab 23	3 372	3 197	20	5	-	87	33	1	-	-	-	-	1	-	-	-	28
Lab 24	6 521	6 167	48	3	232	42	8	1	-	-	-	-	2	-	3	3	12
Lab 25	1 638	1 595	-	-	-	1	6	-	-	-	-	-	-	-	-	-	36
Lab 26	3 792	3 195	251	5	-	3	3	5	-	-	-	-	-	-	-	-	330
Lab 27	4 312	2 718	17	-	116	75	2	-	-	-	-	-	1	-	-	4	1 379
Lab 28	5 670	4 935	367	11	-	216	42	13	13	-	-	-	2	1	3	-	67
Lab 29	6 547	6 121	156	17	-	125	26	5	4	1	-	-	-	-	3	1	88
Lab 30	11 746	10 808	523	147	-	127	35	18	2	1	-	-	-	-	2	-	83
Lab 31	4 442	4 279	118	10	4	20	3	4	-	-	-	-	-	-	-	1	3
Lab 32	4 574	4 420	99	16	2	24	1	4	3	-	-	-	1	-	1	-	3
Lab 33	10 182	9 759	246	21	1	47	28	2	3	-	-	-	1	1	2	1	70
Lab 34	6 035	4 945	525	1	336	28	13	25	12	-	-	-	2	-	-	1	147
Lab 35	6 341	6 087	154	6	-	59	12	6	-	-	-	-	2	-	3	-	12
Lab 36	2 293	2 157	61	4	-	43	16	4	2	-	-	-	-	-	-	-	6
Lab 37	2 320	2 206	45	-	3	45	17	3	1	-	-	-	-	-	-	-	-
Lab 38	1 813	1 648	117	1	3	5	5	22	2	-	-	-	-	-	2	1	7
Lab 39	7 156	6 918	-	-	-	93	127	1	-	-	-	-	-	-	-	9	8
Lab 40	9 285	8 729	273	1	56	27	22	18	154	-	-	-	-	-	-	-	5
Lab 41	12 603	11 522	791	20	-	171	42	21	29	-	1	-	1	1	1	-	3

Lab 42	4 636	4 474	107	10	1	15	11	7	4	-	-	-	-	-	-	-	7
Lab 43	3 782	3 634	78	11	-	28	23	1	-	-	-	-	2	-	-	-	5
Lab 44	12 100	11 874	52	8	29	75	23	4	-	-	-	-	-	-	-	-	35
Lab 45	16 157	15 868	186	11	-	63	23	-	-	-	-	-	-	-	1	-	5
Lab 46	3 229	3 092	82	1	-	24	3	3	2	-	-	-	1	-	-	-	21
Lab 47	6 104	5 866	58	4	1	59	23	2	2	-	-	-	2	-	2	-	85
Lab 48	3 988	3 361	535	16	-	14	14	36	4	-	-	-	-	-	1	-	7
Lab 49	4 523	3 986	43	1	-	63	17	5	-	-	-	-	-	-	-	-	408
Lab 50	6 014	5 925	12	4	-	29	21	1	-	-	-	-	-	-	-	-	22
Lab 51	1 738	1 566	28	6	80	18	5	4	1	-	-	-	-	-	-	-	30
Lab 52	5 323	5 228	11	1	-	32	29	1	-	-	-	-	-	-	-	-	21
Lab 53	11 247	10 647	263	13	-	221	45	12	13	-	-	-	1	1	-	-	31
Lab 54	16 340	14 805	1 050	120	-	4	42	73	-	-	-	-	-	-	-	-	246
Lab 55	18 188	11 200	334	55	5 180	614	91	478	19	1	-	-	10	1	3	1	201
Lab 56	2 186	2 155	10	1	2	15	1	-	-	-	-	-	-	-	-	-	2
Lab 57	4 458	4 314	86	10	-	30	6	4	1	-	-	-	1	-	3	-	3
Lab 58	11 609	8 670	462	1	20	168	64	24	-	-	-	-	2	-	5	-	2 193
Lab 59	7 962	7 119	253	7	4	246	52	90	-	-	-	-	3	-	3	-	185
Lab 60	8 062	7 596	103	6	6	164	34	29	1	-	-	-	4	-	4	-	115
Lab 61	4 409	3 805	231	6	-	185	32	15	2	-	-	-	2	-	-	-	131
Lab 62	2 089	1 988	70	1	-	10	7	5	-	-	-	-	-	-	-	-	8
Total	484 507	427 067	10 501	771	9 865	7 708	1 842	1 405	321	4	1	-	56	13	53	37	24 863
Maximum	76 291	70 968	1 050	147	5 180	2 374	347	478	154	12	10 771	10	4	5	1	1	-
3rdquartile	10 009	8 659	253	11	17	139	34	14	2	-	127	2	-	1	-	-	-
Median	5 842	4 940	81	5	1	47	22	4	1	-	28	-	-	-	-	-	-
1stquartile	3 305	2 812	24	1	-	17	5	2	-	-	7	-	-	-	-	-	-
Minimum	401	30	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-

Table 106 – Frequency of cytological diagnosis (after first readings only) in the CHP (as percentages, year 2011), the method used to analyze cervical smears and the use of an automated system, per laboratory

Laboratory	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN	Liquid based (LB) or conventional (CONV)	Imaginge system used
Lab 1	100.0%	91.5%	2.5%	0.5%	0.0%	2.2%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.9%	LB	HTI
Lab 2	100.0%	96.1%	0.4%	0.0%	0.0%	2.3%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	LB	No
Lab 3	100.0%	98.2%	0.3%	0.1%	0.0%	0.7%	0.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	No
Lab 4	100.0%	90.5%	2.7%	0.0%	6.2%	0.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	Unknown	Unknown
Lab 5	100.0%	96.4%	0.9%	0.1%	0.1%	2.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB	No
Lab 6	100.0%	94.1%	1.8%	0.2%	0.3%	1.5%	0.2%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	1.3%	LB	No
Lab 7	100.0%	90.6%	5.5%	0.7%	0.0%	2.0%	0.4%	0.2%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	HTI
Lab 8	100.0%	89.9%	0.0%	0.0%	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.1%	LB	No
Lab 9	100.0%	88.5%	0.0%	0.0%	1.5%	0.9%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.6%	LB	No
Lab 10	100.0%	94.2%	0.0%	0.0%	3.9%	0.9%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	Unknown	No
Lab 11	100.0%	91.4%	6.6%	0.2%	0.0%	0.4%	0.2%	0.2%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	Unknown	No
Lab 12	100.0%	91.5%	2.3%	0.1%	3.7%	1.0%	0.3%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Unknown	No
Lab 13	100.0%	93.6%	4.9%	0.0%	0.0%	0.4%	0.2%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	Unknown	No
Lab 14	100.0%	96.1%	0.7%	0.0%	0.0%	2.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.2%	LB	No
Lab 15	100.0%	93.0%	0.0%	0.0%	3.2%	3.1%	0.5%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Unknown	HTI
Lab 16	100.0%	93.2%	2.0%	0.1%	0.0%	2.1%	0.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.0%	LB	HTI
Lab 17	100.0%	95.5%	1.2%	0.0%	2.9%	0.1%	0.1%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	LB	Unknown
Lab 18	100.0%	94.8%	2.4%	0.2%	0.0%	0.9%	0.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.2%	LB (50%) + CONV (50%)	Unknown
Lab 19	100.0%	91.3%	4.0%	0.1%	0.0%	3.7%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Unknown	HTI
Lab 20	100.0%	0.3%	3.1%	0.0%	0.1%	1.9%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	94.2%	LB (95%) + CONV (5%)	HTI
Lab 21	100.0%	51.3%	0.9%	0.3%	4.0%	0.0%	0.0%	1.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	42.0%	LB (99%) + CONV (1%)	No
Lab 22	100.0%	96.6%	0.6%	0.2%	0.0%	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	LB (x%) + CONV (x%)	No

Laboratory	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN	Liquid based (LB) or conventional (CONV)	Imaginge system used
Lab 23	100.0%	94.8%	0.6%	0.1%	0.0%	2.6%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	LB	HTI
Lab 24	100.0%	94.6%	0.7%	0.0%	3.6%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB (95%) + CONV (5%)	Unknown
Lab 25	100.0%	97.4%	0.0%	0.0%	0.0%	0.1%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%	LB (95%) + CONV (5%)	No
Lab 26	100.0%	84.3%	6.6%	0.1%	0.0%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.7%	Unknown	Unknown
Lab 27	100.0%	63.0%	0.4%	0.0%	2.7%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	32.0%	CONV	No
Lab 28	100.0%	87.0%	6.5%	0.2%	0.0%	3.8%	0.7%	0.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	1.2%	LB	No
Lab 29	100.0%	93.5%	2.4%	0.3%	0.0%	1.9%	0.4%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.3%	LB	HTI
Lab 30	100.0%	92.0%	4.5%	1.3%	0.0%	1.1%	0.3%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	LB	HTI
Lab 31	100.0%	96.3%	2.7%	0.2%	0.1%	0.5%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	No
Lab 32	100.0%	96.6%	2.2%	0.3%	0.0%	0.5%	0.0%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	No
Lab 33	100.0%	95.8%	2.4%	0.2%	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	LB	HTI
Lab 34	100.0%	81.9%	8.7%	0.0%	5.6%	0.5%	0.2%	0.4%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.4%	LB	Unknown
Lab 35	100.0%	96.0%	2.4%	0.1%	0.0%	0.9%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB	Unknown
Lab 36	100.0%	94.1%	2.7%	0.2%	0.0%	1.9%	0.7%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	No
Lab 37	100.0%	95.1%	1.9%	0.0%	0.1%	1.9%	0.7%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Unknown	No
Lab 38	100.0%	90.9%	6.5%	0.1%	0.2%	0.3%	0.3%	1.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.4%	LB	No
Lab 39	100.0%	96.7%	0.0%	0.0%	0.0%	1.3%	1.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	Unknown	Unknown
Lab 40	100.0%	94.0%	2.9%	0.0%	0.6%	0.3%	0.2%	0.2%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	Unknown	Unknown
Lab 41	100.0%	91.4%	6.3%	0.2%	0.0%	1.4%	0.3%	0.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	LB	No
Lab 42	100.0%	96.5%	2.3%	0.2%	0.0%	0.3%	0.2%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB (x%) + CONV (x%)	No
Lab 43	100.0%	96.1%	2.1%	0.3%	0.0%	0.7%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.1%	LB	Unknown
Lab 44	100.0%	98.1%	0.4%	0.1%	0.2%	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB (x%) + CONV (x%)	HTI

Laboratory	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN	Liquid based (LB) or conventional (CONV)	Imaginge system used
Lab 45	100.0%	98.2%	1.2%	0.1%	0.0%	0.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	LB	BD FocalPoint™ Slide Profiler
Lab 46	100.0%	95.8%	2.5%	0.0%	0.0%	0.7%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	LB	No
Lab 47	100.0%	96.1%	1.0%	0.1%	0.0%	1.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%	LB	No
Lab 48	100.0%	84.3%	13.4%	0.4%	0.0%	0.4%	0.4%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB	No
Lab 49	100.0%	88.1%	1.0%	0.0%	0.0%	1.4%	0.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	9.0%	Unknown	Unknown
Lab 50	100.0%	98.5%	0.2%	0.1%	0.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Unknown	Unknown
Lab 51	100.0%	90.1%	1.6%	0.3%	4.6%	1.0%	0.3%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	CONV	No
Lab 52	100.0%	98.2%	0.2%	0.0%	0.0%	0.6%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Unknown	Unknown
Lab 53	100.0%	94.7%	2.3%	0.1%	0.0%	2.0%	0.4%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	No
Lab 54	100.0%	90.6%	6.4%	0.7%	0.0%	0.0%	0.3%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	LB (x%) + CONV (x%)	No
Lab 55	100.0%	61.6%	1.8%	0.3%	28.5%	3.4%	0.5%	2.6%	0.1%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	1.1%	LB	Unknown
Lab 56	100.0%	98.6%	0.5%	0.0%	0.1%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	Unknown	No
Lab 57	100.0%	96.8%	1.9%	0.2%	0.0%	0.7%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.1%	Unknown	Unknown
Lab 58	100.0%	74.7%	4.0%	0.0%	0.2%	1.4%	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	18.9%	LB	No
Lab 59	100.0%	89.4%	3.2%	0.1%	0.1%	3.1%	0.7%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.3%	Unknown	No
Lab 60	100.0%	94.2%	1.3%	0.1%	0.1%	2.0%	0.4%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%	Unknown	No
Lab 61	100.0%	86.3%	5.2%	0.1%	0.0%	4.2%	0.7%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.0%	LB	Unknown
Lab 62	100.0%	95.2%	3.4%	0.0%	0.0%	0.5%	0.3%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Unknown	No
Total	100.0%	88.1%	2.2%	0.2%	2.0%	1.6%	0.4%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.1%		
Maximum	98.6%	13.4%	1.3%	28.5%	4.2%	1.8%	2.6%	1.7%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	94.2%	Maximum		
3rd quartile	96.1%	3.2%	0.2%	0.2%	1.9%	0.4%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	3rd quartile		
Median	94.1%	2.1%	0.1%	0.0%	0.9%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Median		

Laboratory	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN	Liquid based (LB) or conventional (CONV)	Imaginge system used
1st quartile	90.5%	0.7%	0.0%	0.0%	0.5%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	1st quartile		
Minimum	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Minimum		

HTI: Hologic, ThinPrep Imager

Table 105 and Table 106 show that there is a large variation between laboratories, both in the number of cytological diagnoses and in the percentage of cytological abnormalities. This variation is visualized in the following Box plots (Figure 79).

The funnel plot presented in Figure 80 shows that there is no correlation between the proportion of a cytological diagnosis (in this case: NILM) and the number of samples analyzed per laboratory.

Figure 79 – Box plots: proportion of cytological diagnoses (after first readings only) in the CHP (as percentages, year 2011) per laboratory

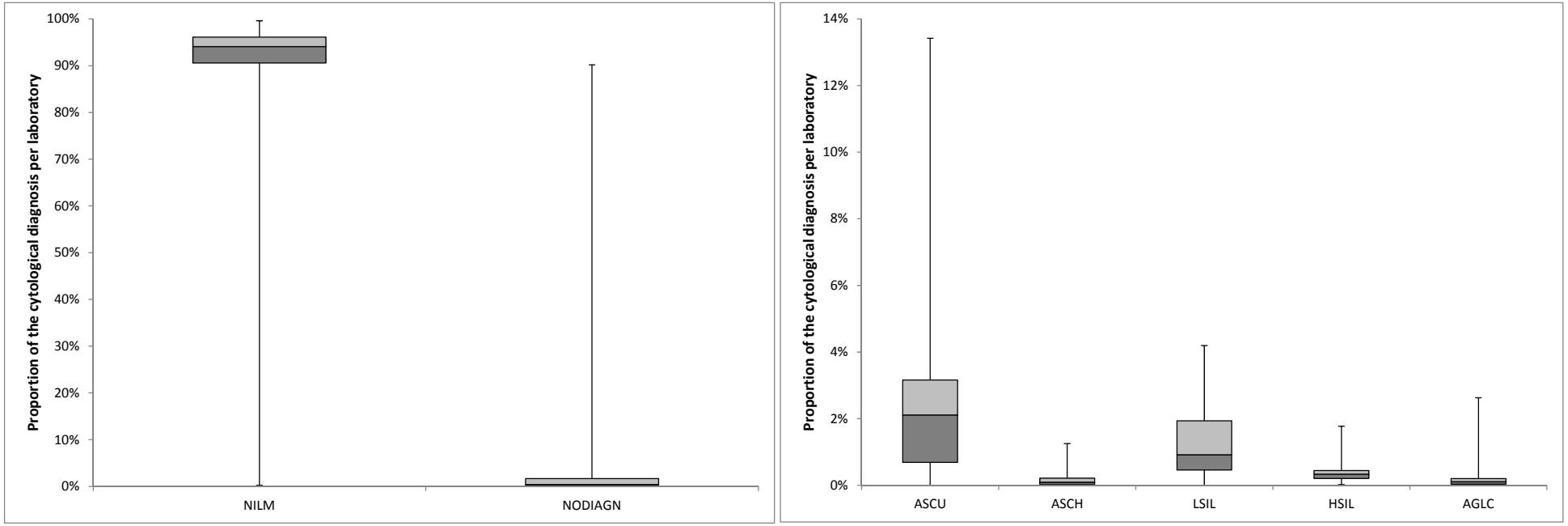
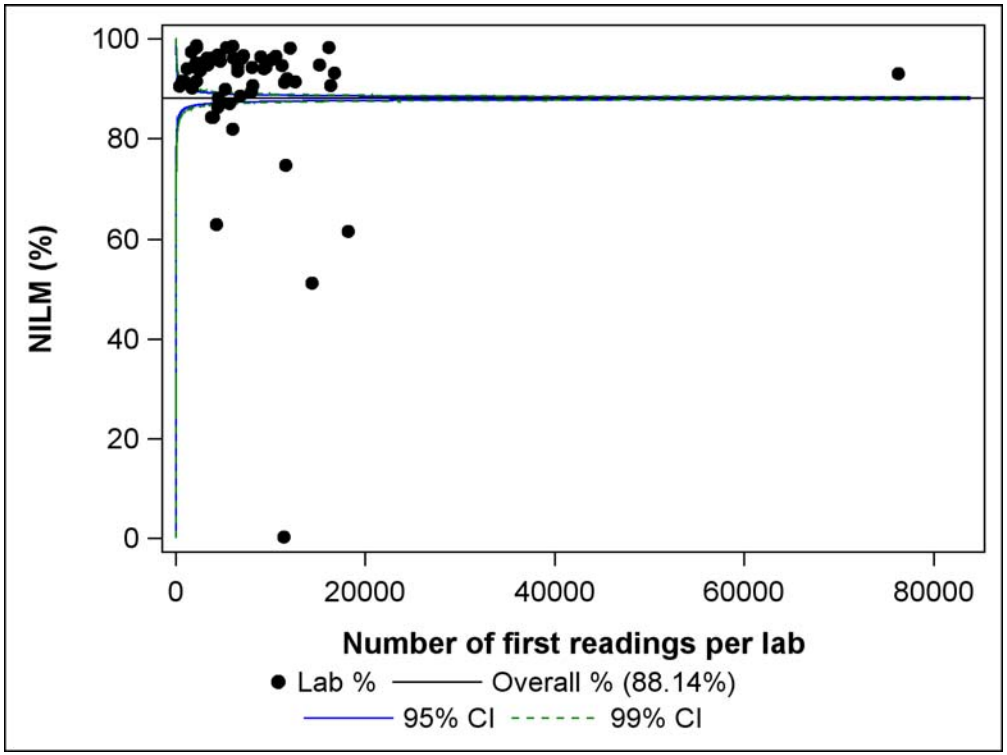


Figure 80 – Funnel plots: frequency of NILM after a first reading in the CHP (as percentages, year 2011) per laboratory, as a function of the number of first readings per laboratory



** Excluding lab 15.*

Table 107 shows the number of and percentages of cytological diagnoses (after first readings only) per type of analysis method used (Liquid based, LB; or conventional, CON). Table 108 shows the number and percentages of ASCU and ATYP (after first readings only) analyzed by Liquid based method with or without the use of an imaging system.

Table 107 – Number and percentages of cytological diagnoses (after first readings only) per type of analysis method (Liquid based, LB; or CON, conventional)

		Liquid based (100%)	LB (99-95%) + CON (5-1%)	LB (50%) + CON (50%)	LB (x%) + CON (x%)	Conventional (100%)	Unknown	Total
	Number of labs	N = 32	N = 4	N = 1	N = 4	N = 2	N = 19	N = 62
Raw numbers (overall)	NILM	197 877	15 179	14 369	41 324	4 284	154 034	427 067
	ASCU	6 463	532	360	1 272	45	1 829	10 501
	ATYP	5 901	820	4	30	196	2 914	9 865
	ASCH	476	45	27	163	6	54	771
	LSIL	3 387	269	143	156	93	3 660	7 708
	HSIL	803	58	62	102	7	810	1 842
	AGLC	762	205	12	89	4	333	1 405
	SQGL	141	5	0	4	1	170	321
	IN SITU*	3	0	0	0	0	1	4
	INVASIVE	77	12	0	0	1	20	110
	OTHER	18	16	1	0	4	11	50
	NODIAGN	4 712	16 864	186	469	1 409	1 223	24 863
	TOTAL	220 620	34 005	15 164	43 609	6 050	165 059	484 507
Percentages (overall)	NILM	89.7%	44.6%	94.8%	94.8%	70.8%	93.3%	88.1%
	ASCU	2.9%	1.6%	2.4%	2.9%	0.7%	1.1%	2.2%
	ATYP	2.7%	2.4%	0.0%	0.1%	3.2%	1.8%	2.0%
	ASCH	0.2%	0.1%	0.2%	0.4%	0.1%	0.0%	0.2%
	LSIL	1.5%	0.8%	0.9%	0.4%	1.5%	2.2%	1.6%
	HSIL	0.4%	0.2%	0.4%	0.2%	0.1%	0.5%	0.4%
	AGLC	0.3%	0.6%	0.1%	0.2%	0.1%	0.2%	0.3%
	SQGL	0.1%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%
	IN SITU*	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	INVASIVE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	OTHER	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%
	NODIAGN	2.1%	49.6%	1.2%	1.1%	23.3%	0.7%	5.1%
	TOTAL	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 108 – Number and percentages of ASCU and ATYP (after first readings only) analyzed by LB with or without the use of an imaging system

		Liquid based (100%)		LB (99-95%) + CON (5-1%)		LB (50%) + CON (50%)		LB (x%) + CON (x%)	
	Imaging system	yes	no	yes	no	yes	no	yes	no
	Number of labs	N = 8	N = 18	N = 1	N = x	N = 0	N = 0	N = 1	N = 3
Raw numbers	ASCU	1 970	3 117	356	128	0	0	52	1 220
	ATYP	3	245	8	580	0	0	29	1
	ASCU + ATYP	1 973	3 362	364	708	0	0	81	1 221
	TOTAL	74 988	102 210	11 437	16 047	0	0	12 100	31 509
Percentages	ASCU	2.6%	3.0%	3.1%	0.8%	0.0%	0.0%	0.4%	3.9%
	ATYP	0.0%	0.2%	0.1%	3.6%	0.0%	0.0%	0.2%	0.0%
	ASCU + ATYP	2.6%	3.3%	3.2%	4.4%	0.0%	0.0%	0.7%	3.9%
	TOTAL	100.0%	100.0%	100.0%	100.0%	0.0%	0.0%	100.0%	100.0%

Table 109 – Explanation of the abbreviation used for the cytological diagnoses

Cytological diagnosis	Meaning
NILM	Negative for intraepithelial lesion of malignancy
ASCU	Atypical squamous cells of undetermined significance
ATYP	Atypical cells, not otherwise specified
ASCH	Atypical squamous cells, cannot exclude HSIL
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
AGLC	Atypical glandular cells
SQGL	Combination of AGLC with either ASCU, ASCH, LSIL or HSIL
ADIS	Adenocarcinoma in situ
ADSQIS	Adenosquamous carcinoma in situ
SQCA	Squamous carcinoma (invasive)
ADCA	Adenocarcinoma (invasive)
ADSQCA	Adenosquamous carcinoma (invasive)
OHTMAL	In situ or invasive tumors, except squamous carcinoma, adenocarcinoma, adenosquamous carcinoma
META	Metastasis in the cervix or tumor invasion of the cervix
NODIAGN	No diagnose

HPV results per laboratory

To evaluate the overall consumption of HPV tests for every cytology sample that is registered in cervix CHP for 2011, it was checked whether a HPV test was performed 30 days after the cytological analyses (first readings only). In order to have a complete view, both CHP and the IMA database were checked for the presence of corresponding HPV records. The total number of HPV tests present in CHP only, in IMA only or present in both databases for 2011, are summarized in Table 110, both as raw numbers (columns 2-5) and percentages (columns 6-9). Results for each individual laboratory are shown. HPV registrations that can only be found in CHP and not in the IMA database represent the non-reimbursed HPV tests (column 2). HPV registrations that can only be found in the IMA database and not in CHP are an indication for the under registration of the HPV result in CHP (column 3).

The total number of HPV records registered in CHP reflects the number of HPV test with a known diagnosis (column 10). This total number of HPV tests in CHP is also represented as percentage of the total number of HPV tests in CHP and IMA (column 11). This percentage is an indication of the completeness of the registration of the HPV test results by the laboratories.

Table 110 – Number of HPV tests performed after cytology (first readings only) according to the IMA data and/or CHP, number of HPV tests registered in the CHP per laboratory (raw numbers and as percentages, year 2011). For each laboratory is indicated which laboratory performs the HPV test and which test is used

	HPV performed after first reading (30days) according to IMA data and/or CHP								HPV performed after first reading (30d) and registered in CHP			Which test is used for HPV detection?	
Laboratory (1)	HPV from CHP only (2)	HPV from IMA only (3)	HPV from CHP AND IMA (4)	TOTAL HPV (from CHP and/or IMA) (5)	HPV from CHP only (6)	HPV from IMA only (7)	HPV from CHP AND IMA (8)	TOTAL HPV (from CHP and/or IMA) (9)	TOTAL HPV from CHP (10)	TOTAL HPV from CHP (/ TOTAL HPV) (11)	Which laboratory performs the HPV tests? (12)	Firm (13)	Type of HPV test used (14)
Lab 1	40	3	74	117	34.2%	2.6%	63.2%	100.0%	114	97.4%	Ohter pathology lab	Roche	Linear array HPV genotyping test
Lab 2	39	-	-	39	100.0%	0.0%	0.0%	100.0%	39	100.0%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 3	9	-	5	14	64.3%	0.0%	35.7%	100.0%	14	100.0%	Clinical lab	Qiagen	digene HC2 HR HPV DNA test
Lab 4	4	-	-	4	100.0%	0.0%	0.0%	100.0%	4	100.0%	Unknown	Unknown	Unknown
Lab 5	-	42	4	46	0.0%	91.3%	8.7%	100.0%	4	8.7%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 6	33	-	-	33	100.0%	0.0%	0.0%	100.0%	33	100.0%	Ohter pathology lab	Unknown	Unknown
Lab 7	73	-	446	519	14.1%	0.0%	85.9%	100.0%	519	100.0%	Unknown	Qiagen bioMérieux for positive samples	Digene HC2 HR HPV DNA test NucliSENS EasyQ HPV
Lab 8	96	-	1	97	99.0%	0.0%	1.0%	100.0%	97	100.0%	Pathology lab itself	Unknown	Unknown
Lab 9	36	-	79	115	31.3%	0.0%	68.7%	100.0%	115	100.0%	Ohter pathology lab	Roche	Linear array HPV genotyping test
Lab 10	18	5	358	381	4.7%	1.3%	94.0%	100.0%	376	98.7%	Unknown	Unknown	Unknown

Lab 11	3	7	34	44	6.8%	15.9%	77.3%	100.0%	37	84.1%	Unknown	Unknown	Unknown
Lab 12	-	22	2	24	0.0%	91.7%	8.3%	100.0%	2	8.3%	Unknown	Unknown	Unknown
Lab 13	6	6	110	122	4.9%	4.9%	90.2%	100.0%	116	95.1%	Unknown	Unknown	Unknown
Lab 14	11	-	14	25	44.0%	0.0%	56.0%	100.0%	25	100.0%	Clinical lab own hospital	Qiagen	Digene HC2 HPV DNA test
Lab 15	73 367	2	2567	75 936	96.6%	0.0%	3.4%	100.0%	75,934	100.0%	Pathology lab itself	AML	AML probe
Lab 16	30	-	332	362	8.3%	0.0%	91.7%	100.0%	362	100.0%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 17	47	-	-	47	100.0%	0.0%	0.0%	100.0%	47	100.0%	Pathology lab itself	DAKO	Immuno histochemistry
Lab 18	38	33	123	194	19.6%	17.0%	63.4%	100.0%	161	83.0%	Pathology lab itself	Hologic	Cervista HPV HR
Lab 19	52	11	414	477	10.9%	2.3%	86.8%	100.0%	466	97.7%	Ohter pathology lab	Roche	Cobas
Lab 20	24	-	17	41	58.5%	0.0%	41.5%	100.0%	41	100.0%	Pathology lab itself	Roche	Cobas
Lab 21	386	1	1	388	99.5%	0.3%	0.3%	100.0%	387	99.7%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 22	20	52	2	74	27.0%	70.3%	2.7%	100.0%	22	29.7%	Ohter pathology lab	Hologic	Cervista HPV HR
Lab 23	3	1	23	27	11.1%	3.7%	85.2%	100.0%	26	96.3%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 24	165	6	52	223	74.0%	2.7%	23.3%	100.0%	217	97.3%	Ohter pathology lab	Abbott AML	Abbot RealTime HR HPV AML probe
Lab 25	-	21	1	22	0.0%	95.5%	4.5%	100.0%	1	4.5%	Ohter pathology lab	Qiagen	Digene HC2 HPV DNA test
Lab 26	4	-	1	5	80.0%	0.0%	20.0%	100.0%	5	100.0%	Unknown	Unknown	Unknown
Lab 27	8	1	-	9	88.9%	11.1%	0.0%	100.0%	8	88.9%	Clinical lab	Abbott	Abbot RealTime HR HPV
Lab 28	133	-	354	487	27.3%	0.0%	72.7%	100.0%	487	100.0%	Pathology lab itself	Hologic	Cervista HPV HR
Lab 29	22	4	138	164	13.4%	2.4%	84.1%	100.0%	160	97.6%	Ohter pathology lab	Roche	Linear array HPV genotyping test
Lab 30	82	-	617	699	11.7%	0.0%	88.3%	100.0%	699	100.0%	Pathology lab itself	Roche	Amplicor
Lab 31	5	13	113	131	3.8%	9.9%	86.3%	100.0%	118	90.1%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 32	6	2	113	121	5.0%	1.7%	93.4%	100.0%	119	98.3%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 33	55	5	296	356	15.4%	1.4%	83.1%	100.0%	351	98.6%	Pathology lab itself	Roche	Linear array HPV genotyping test

Lab 34	61	296	541	898	6.8%	33.0%	60.2%	100.0%	602	67.0%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 35	4	6	154	164	2.4%	3.7%	93.9%	100.0%	158	96.3%	Clinical lab own hospital	Qiagen	digene HC2 HPV DNA test
Lab 36	61	2	66	129	47.3%	1.6%	51.2%	100.0%	127	98.4%	Clinical lab own hospital	Greiner Bio One	PapilloCheck
Lab 37	70	-	49	119	58.8%	0.0%	41.2%	100.0%	119	100.0%	Unknown	Unknown	Unknown
Lab 38	-	17	87	104	0.0%	16.3%	83.7%	100.0%	87	83.7%	Clinical lab	Roche	Cobas
Lab 39	4	4	5	13	30.8%	30.8%	38.5%	100.0%	9	69.2%	Unknown	Unknown	Unknown
Lab 40	5	357	196	558	0.9%	64.0%	35.1%	100.0%	201	36.0%	Clinical lab own hospital	Roche	Cobas
Lab 41	27	5	833	865	3.1%	0.6%	96.3%	100.0%	860	99.4%	Clinical lab own hospital	Abbott Microgen Bioproducts	Abbot RealTime HR HPV INNO-LiPA HPV genotypering
Lab 42	15	1	11	27	55.6%	3.7%	40.7%	100.0%	26	96.3%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 43	22	1	71	94	23.4%	1.1%	75.5%	100.0%	93	98.9%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 44	20	10	38	68	29.4%	14.7%	55.9%	100.0%	58	85.3%	Pathology lab itself	Roche	Linear array HPV genotyping test
Lab 45	54	2	176	232	23.3%	0.9%	75.9%	100.0%	230	99.1%	Clinical lab own hospital	Qiagen	digene HC2 HPV DNA test
Lab 46	-	11	3	14	0.0%	78.6%	21.4%	100.0%	3	21.4%	Clinical lab	Roche	Amplicor
Lab 47	10	-	57	67	14.9%	0.0%	85.1%	100.0%	67	100.0%	Ohter pathology lab	AML	AML probe
Lab 48	38	35	491	564	6.7%	6.2%	87.1%	100.0%	529	93.8%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 49	43	23	19	85	50.6%	27.1%	22.4%	100.0%	62	72.9%	Unknown	Unknown	Unknown
Lab 50	-	-	-	-	NA	NA	NA	NA	-	NA	Unknown	Unknown	Unknown
Lab 51	1	1	2	4	25.0%	25.0%	50.0%	100.0%	3	75.0%	Ohter pathology lab	Roche	Cobas
Lab 52	15	-	9	24	62.5%	0.0%	37.5%	100.0%	24	100.0%	Unknown	Unknown	Unknown
Lab 53	63	-	249	312	20.2%	0.0%	79.8%	100.0%	312	100.0%	Ohter pathology lab	Qiagen	digene HC2 HPV DNA test
Lab 54	283	-	-	283	100.0%	0.0%	0.0%	100.0%	283	100.0%	Clinical lab own hospital	bioMérieux	NucliSENS EasyQ HPV
Lab 55	247	-	341	588	42.0%	0.0%	58.0%	100.0%	588	100.0%	Pathology lab itself	Qiagen	digene HC2 HPV DNA test

Lab 56	1	6	1	8	12.5%	75.0%	12.5%	100.0%	2	25.0%	Clinical hospital	lab	own	Unknown	Unknown
Lab 57	22	1	86	109	20.2%	0.9%	78.9%	100.0%	108	99.1%	Unknown			Unknown	Unknown
Lab 58	23	112	410	545	4.2%	20.6%	75.2%	100.0%	433	79.4%	Clinical hospital	lab	own	Unknown	Unknown
Lab 59	96	8	247	351	27.4%	2.3%	70.4%	100.0%	343	97.7%	Clinical hospital	lab	own	Unknown	Unknown
Lab 60	7	31	78	116	6.0%	26.7%	67.2%	100.0%	85	73.3%	Clinical hospital	lab	own	Unknown	Unknown
Lab 61	6	1	189	196	3.1%	0.5%	96.4%	100.0%	195	99.5%	Ohter pathology lab			Unknown	Unknown
Lab 62	5	37	27	69	7.2%	53.6%	39.1%	100.0%	32	46.4%	Unknown			bioMérieux	NucliSENS EasyQ HPV
Total	76 018	1204	10 727	87 949	86.4%	1.4%	12.2%	100.0%	86,745	98.6%					

HPV tests can be performed in the pathology laboratory itself. However, the samples are often sent to another laboratory. This can be either another pathology laboratory that has the ability to perform HPV tests, or a clinical laboratory. Pathology laboratories connected to a hospital send their HPV tests in most cases to the clinical laboratory affiliated to the same hospital. To have a view on this, it was asked to the laboratories where the HPV tests were performed. The results of this questionnaire are also listed in Table 42 (column 12). In the last two columns is indicated which HPV test is used.

Correlation between cytological and HPV results per laboratory (for ASCU / ATYP diagnoses)

In this section we want to investigate on how much a HPV test was done on cytological samples with a diagnosis of ASCU and also the result of this HPV test. Section 5.1.2 shows that there are large differences between laboratories in the percentage of ASCU on the total number of smears. On the one hand, this can be due to inter-individual differences among pathologists in the evaluation of the smears. On the other hand, this can be a cause of the quality of coding. Often, it is indicated that atypical cells are present, without specifying if cells are squamous or glandular. These samples are thus diagnosed as ATYP. Since these atypical cells are most likely squamous cells, the number of ATYP-diagnoses was added to the number of ASCU-diagnoses for further analysis. In Table 111, the total number of cytological samples (first readings only; column 2), the number of ASCU (column 3), the number of ATYP (column 4) and the sum of ASCU and ATYP (column 5) is shown per laboratory. The percentage of ASCU and ATYP diagnoses compared to the total number of cytological samples in CHP was calculated (column 6).

HPV tests which are registered in the CHP and/or IMA database were determined and calculated per laboratory (column 7), so that the% of cytological samples followed by a HPV test could be determined (column 8). Both the percentage of ASCU + ATYP (column 6) and the percentage of samples on which a HPV detection is performed (column 8) varies from laboratory to laboratory, as shown in Figures 27-28. The percentage of all cytological samples with a ASCU/ATYP diagnosis where HPV-detection was performed is shown in column 12. The absolute numbers are given in column 9-11. The% of these HPV tests which were positive are given in column 16. The corresponding absolute numbers are given in column 13-15. For laboratories where less than 60% of HPV-results are registered in CHP, the percentage of HPV-positive ASCU/ATYP is not reliable (see Table 42, column 11). It concerns the following laboratories: Lab 5, Lab 12, Lab 22, Lab 25, Lab 40, Lab 46 , Lab 50 , Lab 56 and Lab 62. The non-reliable percentages of these laboratories are marked with an asterisk (*). The percentage of HPV-positive after ASCU/ATYP for Lab 39, Lab 51 and Lab 52 is also not reliable, due to the small number of HPV-detections that was performed on the ASCU/ATYP cytological samples and is marked with a double asterisk (**). On average, the numbers of HPV tests that are performed on an ASCU/ATYP are

39.95% positive. If the twelve less reliable laboratories are not included in the calculation, this average lies slightly higher at 41.25%. However, there are large differences between laboratories, with values between 15.68% (Lab 34) and 100.00% (Lab 27). This is also illustrated in the box plots and correlation plots below (Figure 81, Figure 82, Figure 83, Figure 84, Figure 85).

Table 111 – Overview table of ASCU / ATYP diagnoses (after first readings only; columns 2-6), HPV tests registered in CHP and / or IMA (columns 7-8), HPV tests performed on ASCU/ATYP (columns 9-12) and HPV positive ASCU / ATYP (columns 13-16) (raw numbers and as percentages, year 2011)

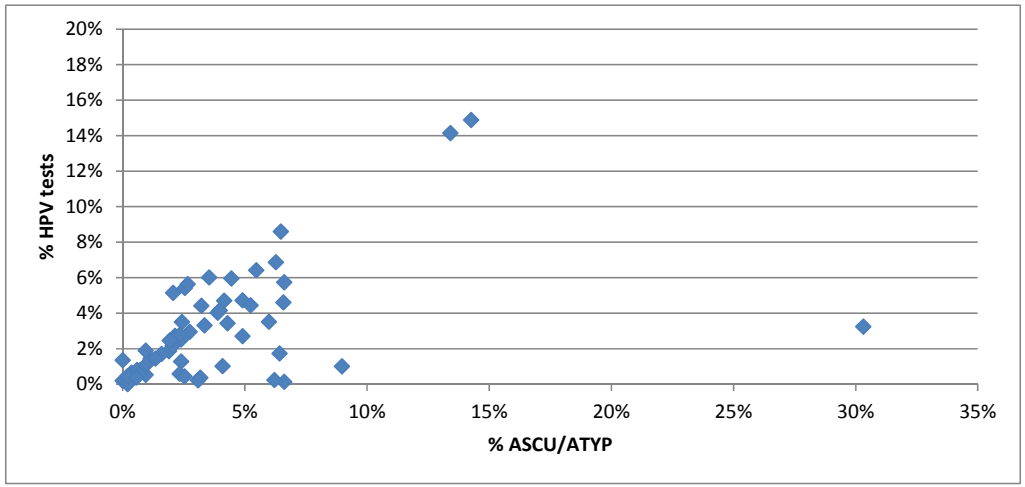
	ASCU / ATYP diagnoses					HPV tests registered		HPV tests performed on ASCU/ATYP				HPV positive ASCU / ATYP			
Laboratory (1)	TOTAL first readings (from CHP) (2)	ASCU (3)	ATYP (4)	ASCU + ATYP (5)	% ASCU+ATYP (/TOTAL first readings) (6)	TOTAL HPV (CHP and/or IMA) (7)	% TOTAL HPV (/TOTAL first readings) (8)	TOTAL HPV (CHP and/or IMA) after ASCU (9)	TOTAL HPV (CHP and/or IMA) after ATYP (10)	TOTAL HPV (CHP and/or IMA) after ASCU or ATYP (11)	% TOTAL HPV after ASCU or ATYP (/TOTAL ASCU+ATYP) (12)	HPV+ from CHP after ASCU (13)	HPV+ from CHP after ATYP (14)	TOTAL HPV+ from CHP after ASCU or ATYP (15)	% TOTAL HPV+ after HPV on ASCU or ATYP (/TOTAL HPV on ASCU+ATYP)
Lab 1	2 162	55	-	55	2.54%	117	5.51%	50	-	50	90.91%	24	-	24	48.00%
Lab 2	7 004	30	-	30	0.43%	39	0.56%	23	-	23	76.67%	14	-	14	60.87%
Lab 3	2 191	7	1	8	0.37%	14	0.64%	6	-	6	75.00%	3	-	3	50.00%
Lab 4	401	11	25	36	8.98%	4	1.00%	3	-	3	8.33%	1	-	1	33.33%
Lab 5	8 945	80	5	85	0.95%	46	0.51%	40	-	40	47.06%	1	-	1	*2.50%
Lab 6	1 214	22	4	26	2.14%	33	2.72%	19	3	22	84.62%	11	1	12	54.55%
Lab 7	8 093	443	-	443	5.47%	519	6.41%	422	-	422	95.26%	95	-	95	22.51%
Lab 8	5 208	-	99	99	1.90%	97	1.86%	-	84	84	84.85%	-	50	50	59.52%
Lab 9	6 794	3	105	108	1.59%	115	1.69%	3	88	91	84.26%	2	38	40	43.96%
Lab 10	9 489	-	369	369	3.89%	381	4.02%	-	361	361	97.83%	-	135	135	37.40%
Lab 11	957	63	-	63	6.58%	44	4.60%	34	-	34	53.97%	10	-	10	29.41%
Lab 12	684	16	25	41	5.99%	24	3.51%	16	-	16	39.02%	1	-	1	*6.25%
Lab 13	2 587	126	1	127	4.91%	122	4.72%	105	1	106	83.46%	41	1	42	39.62%

	ASCU / ATYP diagnoses					HPV tests registered		HPV tests performed on ASCU/ATYP				HPV positive ASCU / ATYP			
Laboratory (1)	TOTAL first readings (from CHP) (2)	ASCU (3)	ATYP (4)	ASCU + ATYP (5)	% ASCU+ATYP (/TOTAL first readings) (6)	TOTAL HPV (CHP and/or IMA) (7)	% TOTAL HPV (/TOTAL first readings) (8)	TOTAL HPV (CHP and/or IMA) after ASCU (9)	TOTAL HPV (CHP and/or IMA) after ATYP (10)	TOTAL HPV (CHP and/or IMA) after ASCU or ATYP (11)	% TOTAL HPV after ASCU or ATYP (/TOTAL ASCU+ATYP) (12)	HPV+ from CHP after ASCU (13)	HPV+ from CHP after ATYP (14)	TOTAL HPV+ from CHP after ASCU or ATYP (15)	% TOTAL HPV+ after HPV on ASCU or ATYP (/TOTAL HPV on ASCU+ATYP)
Lab 14	3 282	22	1	23	0.70%	25	0.76%	19	1	20	86.96%	14	-	14	70.00%
Lab 15	76 291	-	2 423	2 423	3.18%	75 936	99.53%	-	2 423	2 423	100.0%	-	1 729	1 729	71.36%
Lab 16	16 729	341	2	343	2.05%	362	2.16%	340	2	342	99.71%	96	1	97	28.36%
Lab 17	4 667	54	137	191	4.09%	47	1.01%	19	6	25	13.09%	5	-	5	20.00%
Lab 18	15 164	360	4	364	2.40%	194	1.28%	153	-	153	42.03%	46	-	46	30.07%
Lab 19	11 480	456	-	456	3.97%	477	4.16%	426	-	426	93.42%	102	-	102	23.94%
Lab 20	11 437	356	8	364	3.18%	41	0.36%	30	1	31	8.52%	15	1	16	51.61%
Lab 21	14 409	128	580	708	4.91%	388	2.69%	116	17	133	18.79%	34	11	45	33.83%
Lab 22	10 533	63	-	63	0.60%	74	0.70%	42	-	42	66.67%	2	-	2	*4.76%
Lab 23	3 372	20	-	20	0.59%	27	0.80%	18	-	18	90.00%	8	-	8	44.44%
Lab 24	6 521	48	232	280	4.29%	223	3.42%	29	85	114	40.71%	15	42	57	50.00%
Lab 25	1 638	-	-	-	0.00%	22	1.34%	-	-	-	NA	-	-	-	*NA
Lab 26	3 792	251	-	251	6.62%	5	0.13%	3	-	3	1.20%	2	-	2	66.67%
Lab 27	4 312	17	116	133	3.08%	9	0.21%	-	1	1	0.75%	-	1	1	100.0%
Lab 28	5 670	367	-	367	6.47%	487	8.59%	359	-	359	97.82%	109	-	109	30.36%
Lab 29	6 547	156	-	156	2.38%	164	2.50%	126	-	126	80.77%	54	-	54	42.86%
Lab 30	11 746	523	-	523	4.45%	699	5.95%	521	-	521	99.62%	200	-	200	38.39%
Lab 31	4 442	118	4	122	2.75%	131	2.95%	117	-	117	95.90%	60	-	60	51.28%

	ASCU / ATYP diagnoses					HPV tests registered		HPV tests performed on ASCU/ATYP					HPV positive ASCU / ATYP		
Laboratory (1)	TOTAL first readings (from CHP) (2)	ASCU (3)	ATYP (4)	ASCU + ATYP (5)	% ASCU+ATYP (/TOTAL first readings) (6)	TOTAL HPV (CHP and/or IMA) (7)	% TOTAL HPV (/TOTAL first readings) (8)	TOTAL HPV (CHP and/or IMA) after ASCU (9)	TOTAL HPV (CHP and/or IMA) after ATYP (10)	TOTAL HPV (CHP and/or IMA) after ASCU or ATYP (11)	% TOTAL HPV after ASCU or ATYP (/TOTAL ASCU+ATYP) (12)	HPV+ from CHP after ASCU (13)	HPV+ from CHP after ATYP (14)	TOTAL HPV+ from CHP after ASCU or ATYP (15)	% TOTAL HPV+ after HPV on ASCU or ATYP (/TOTAL HPV on ASCU+ATYP)
Lab 32	4 574	99	2	101	2.21%	121	2.65%	98	-	98	97.03%	47	-	47	47.96%
Lab 33	10 182	246	1	247	2.43%	356	3.50%	244	-	244	98.79%	129	-	129	52.87%
Lab 34	6 035	525	336	861	14.27%	898	14.88%	522	288	810	94.08%	127	-	127	15.68%
Lab 35	6 341	154	-	154	2.43%	164	2.59%	153	-	153	99.35%	62	-	62	40.52%
Lab 36	2 293	61	-	61	2.66%	129	5.63%	60	-	60	98.36%	17	-	17	28.33%
Lab 37	2 320	45	3	48	2.07%	119	5.13%	44	3	47	97.92%	21	1	22	46.81%
Lab 38	1 813	117	3	120	6.62%	104	5.74%	81	-	81	67.50%	14	-	14	17.28%
Lab 39	7 156	-	-	-	0.00%	13	0.18%	-	-	-	NA	-	-	-	**NA
Lab 40	9 285	273	56	329	3.54%	558	6.01%	259	52	311	94.53%	30	10	40	*12.86%
Lab 41	12 603	791	-	791	6.28%	865	6.86%	786	-	786	99.37%	214	-	214	27.23%
Lab 42	4 636	107	1	108	2.33%	27	0.58%	13	-	13	12.04%	8	-	8	61.54%
Lab 43	3 782	78	-	78	2.06%	94	2.49%	74	-	74	94.87%	34	-	34	45.95%
Lab 44	12 100	52	29	81	0.67%	68	0.56%	39	7	46	56.79%	26	7	33	71.74%
Lab 45	16 157	186	-	186	1.15%	232	1.44%	183	-	183	98.39%	147	-	147	80.33%
Lab 46	3 229	82	-	82	2.54%	14	0.43%	12	-	12	14.63%	1	-	1	*8.33%
Lab 47	6 104	58	1	59	0.97%	67	1.10%	55	-	55	93.22%	16	-	16	29.09%
Lab 48	3 988	535	-	535	13.42%	564	14.14%	499	-	499	93.27%	97	-	97	19.44%
Lab 49	4 523	43	-	43	0.95%	85	1.88%	36	-	36	83.72%	13	-	13	36.11%
Lab 50	6 014	12	-	12	0.20%	-	0.00%	-	-	-	0.00%	-	-	-	*NA

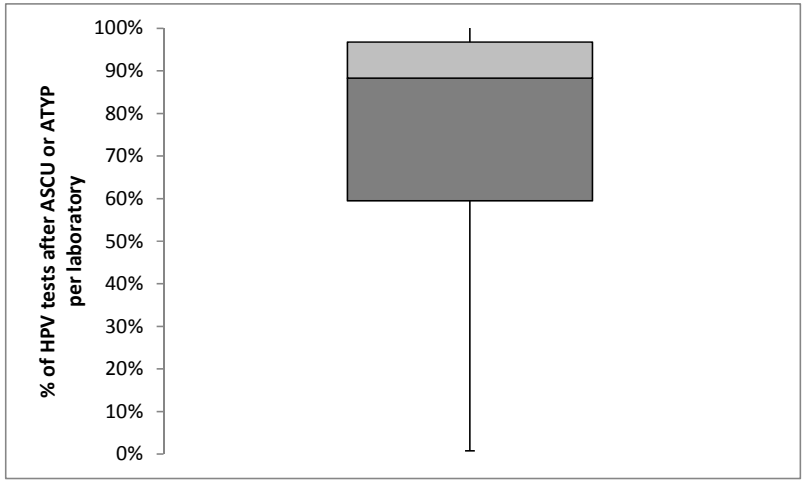
	ASCU / ATYP diagnoses					HPV tests registered		HPV tests performed on ASCU/ATYP				HPV positive ASCU / ATYP			
Laboratory (1)	TOTAL first readings (from CHP) (2)	ASCU (3)	ATYP (4)	ASCU + ATYP (5)	% ASCU+ATYP (/TOTAL first readings) (6)	TOTAL HPV (CHP and/or IMA) (7)	% TOTAL HPV (/TOTAL first readings) (8)	TOTAL HPV (CHP and/or IMA) after ASCU (9)	TOTAL HPV (CHP and/or IMA) after ATYP (10)	TOTAL HPV (CHP and/or IMA) after ASCU or ATYP (11)	% TOTAL HPV after ASCU or ATYP (/TOTAL ASCU+ATYP) (12)	HPV+ from CHP after ASCU (13)	HPV+ from CHP after ATYP (14)	TOTAL HPV+ from CHP after ASCU or ATYP (15)	% TOTAL HPV+ after HPV on ASCU or ATYP (/TOTAL HPV on ASCU+ATYP)
Lab 51	1 738	28	80	108	6.21%	4	0.23%	1	-	1	0.93%	-	-	-	**0.00%
Lab 52	5 323	11	-	11	0.21%	24	0.45%	-	-	-	0.00%	-	-	-	**NA
Lab 53	11 247	263	-	263	2.34%	312	2.77%	258	-	258	98.10%	112	-	112	43.41%
Lab 54	16 340	1 050	-	1 050	6.43%	283	1.73%	247	-	247	23.52%	62	-	62	25.10%
Lab 55	18 188	334	5 180	5 514	30.32%	588	3.23%	301	56	357	6.47%	155	25	180	50.42%
Lab 56	2 186	10	2	12	0.55%	8	0.37%	7	-	7	58.33%	1	-	1	*14.29%
Lab 57	4 458	86	-	86	1.93%	109	2.45%	77	-	77	89.53%	43	-	43	55.84%
Lab 58	11 609	462	20	482	4.15%	545	4.69%	417	20	437	90.66%	115	4	119	27.23%
Lab 59	7 962	253	4	257	3.23%	351	4.41%	234	4	238	92.61%	46	-	46	19.33%
Lab 60	8 062	103	6	109	1.35%	116	1.44%	88	4	92	84.40%	21	-	21	22.83%
Lab 61	4 409	231	-	231	5.24%	196	4.45%	157	-	157	67.97%	29	-	29	18.47%
Lab 62	2 089	70	-	70	3.35%	69	3.30%	65	-	65	92.86%	8	-	8	*12.31%
Total	484 507	10 501	9 865	20 366	4.20%	87 949	18.15%	8 049	3 507	11 556	56.74%	2 560	2 057	4 617	39.95%

Figure 81 – Correlation between the percentage of ASCU+ATYP and the percentage of HPV tests per total number of cytology samples (first readings only)



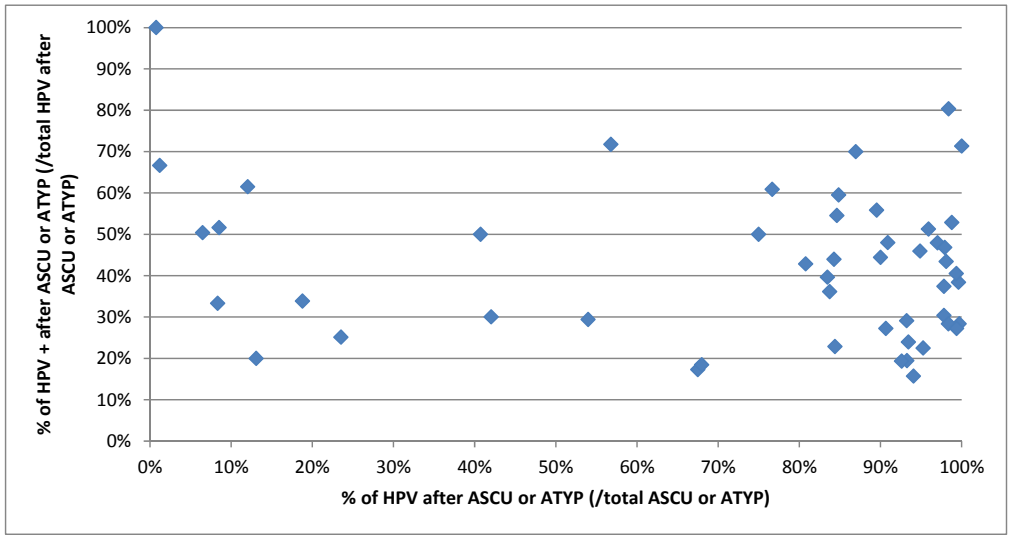
Laboratory 15 has been omitted from this figure.

Figure 82 – Box plot: frequency of HPV tests after ASCU/ATYP in the CHP (as percentages, year 2011) per laboratory



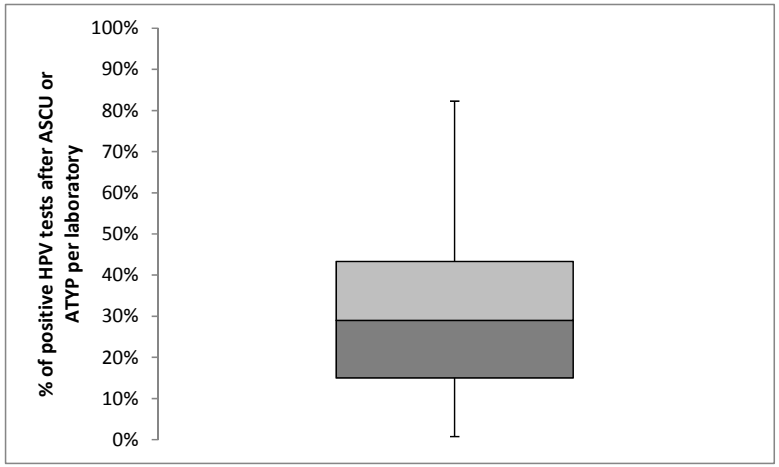
The twelve less reliable laboratories were not included in the box plot.

Figure 83 – Correlation between the percentage of positive HPV after ASCU/ATYP (in CHP) and the percentage of HPV tests (in IMA and/or CHP) performed after ASCU/ATYP



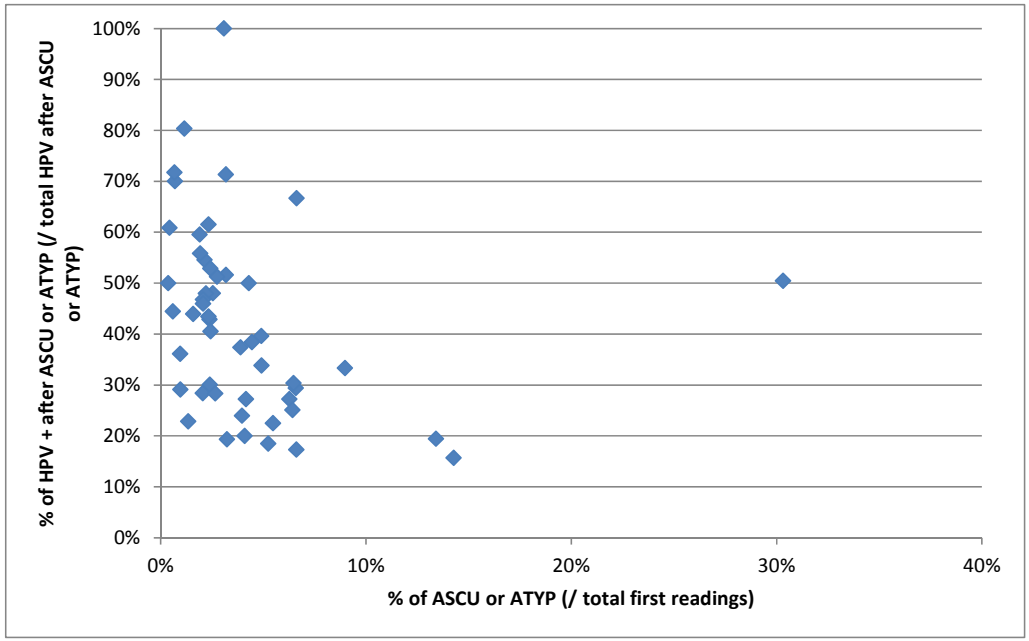
The twelve less reliable laboratories were not included in the correlation plot.

Figure 84 – Box plot: frequency of positive HPV tests after ASCU/ATYP in the CHP (as percentages, year 2011) per laboratory



The twelve less reliable laboratories were not included in the box plot.

Figure 85 – Correlation between the percentage of positive HPV after ASCU/ATYP (in CHP) and the percentage of ASCU/ATYP (in CHP)



The twelve less reliable laboratories were not included in the correlation plot.

Appendix 1.1.5.2. Correlation cytology-histology

In this section the correlation between an abnormal cytological diagnosis (of first readings only) and the first subsequent biopsy is investigated.

Firstly, the duration between a histological examination and the preceding smear in CHP for 2011 was evaluated (Figure 86). A considerable number of biopsies were taken on the same day than a smear. The majority of the biopsies were taken within 3 months after a smear. To evaluate the correlation between the cytological diagnosis and the first subsequent biopsy, a time delay of 3 months between both medical acts was selected.

Figure 86 – Frequency of the time delay between a histological examination and the preceding smear (first reading only) as registered in the CHP (year 2011)

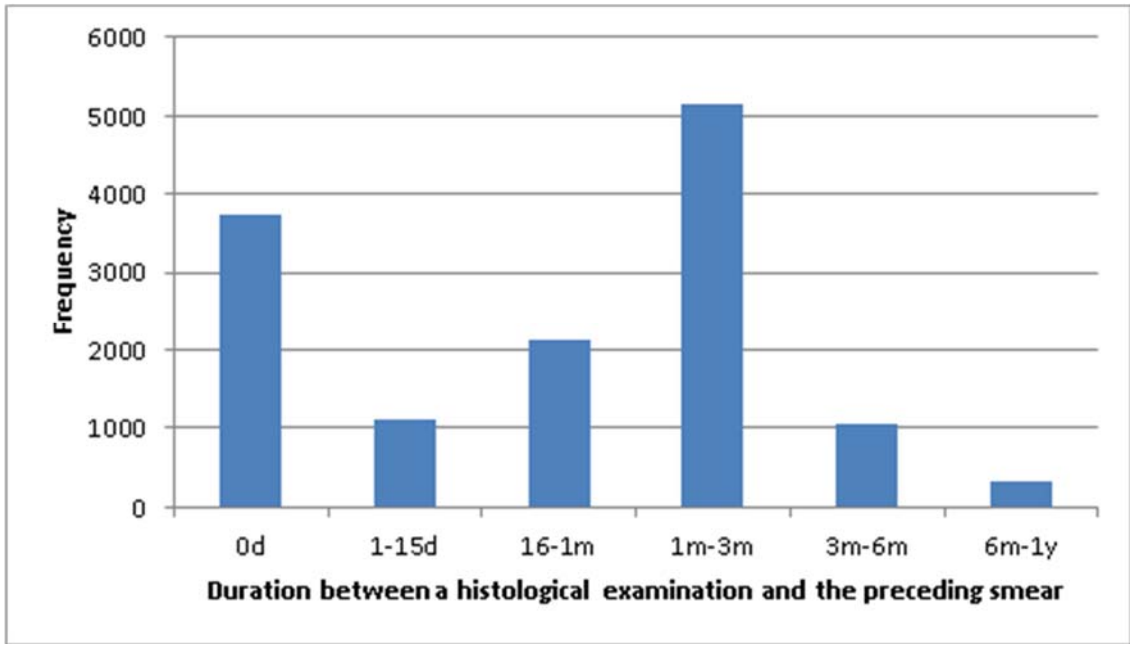


Table 112 and Figure 87 show the correlation between cytological diagnosis and the first subsequent histological diagnosis within a time delay of 3 months. Biopsies taken on the same day as the smear were included. The histological diagnoses are subdivided into negative samples (ABST/NODIAGN), samples with atypical cells, glandular lesions and lesions with CIN1 or worse (CIN1+). The category CIN1+ are further subdivided into the categories CIN2+ (CIN2 or worse) and CIN3+ (CIN3 or worse). All lesions that are included in the categories CIN1+, CIN2+ and CIN3+ are mentioned under Table 112. The significations of the histological diagnoses are listed in Table 113.

Table 112 – Correlation between the cytological diagnosis (after first readings only) and the first subsequent histological diagnosis within a time delay of between 0 day and 3 months

	Histological diagnosis						
Cytological diagnosis	**ABST*/NODIAGN**	**ATYP**	**Glandular lesion (*)**	**CIN1+ (†)**	**Total**	**CIN2+ (††)**	**CIN3+ (†††)**
NILM	3 358	37	1	314	3 710	131	76
NODIAGN	381	33	0	209	623	125	66
ASCU/ATYP	1 221	78	0	1 376	2 675	507	239
ASCH	131	12	0	222	365	154	85
LSIL	777	30	0	1 544	2 351	520	151
HSIL	370	21	5	1 641	2 037	1 370	839
AGLC	106	6	1	49	162	30	23
SQGL	33	1	0	58	92	36	23
IN SITU/INVASIVE	7	0	0	75	82	74	72
Total	6 384	218	7	5 488	12 097	2 947	1 574

(*) includes CGIN, SQGL.
(†) includes CIN1, CIN2, SQIS, ADIS, ADSQIS, SQCA, ADCA, ADSQCA, OTHMAL, META.
(††) includes CIN2, SQIS, ADIS, ADSQIS, SQCA, ADCA, ADSQCA, OTHMAL, META.
(†††) includes SQIS, ADIS, ADSQIS, SQCA, ADCA, ADSQCA, OTHMAL, META.

Table 113 – Meaning of the histological diagnoses

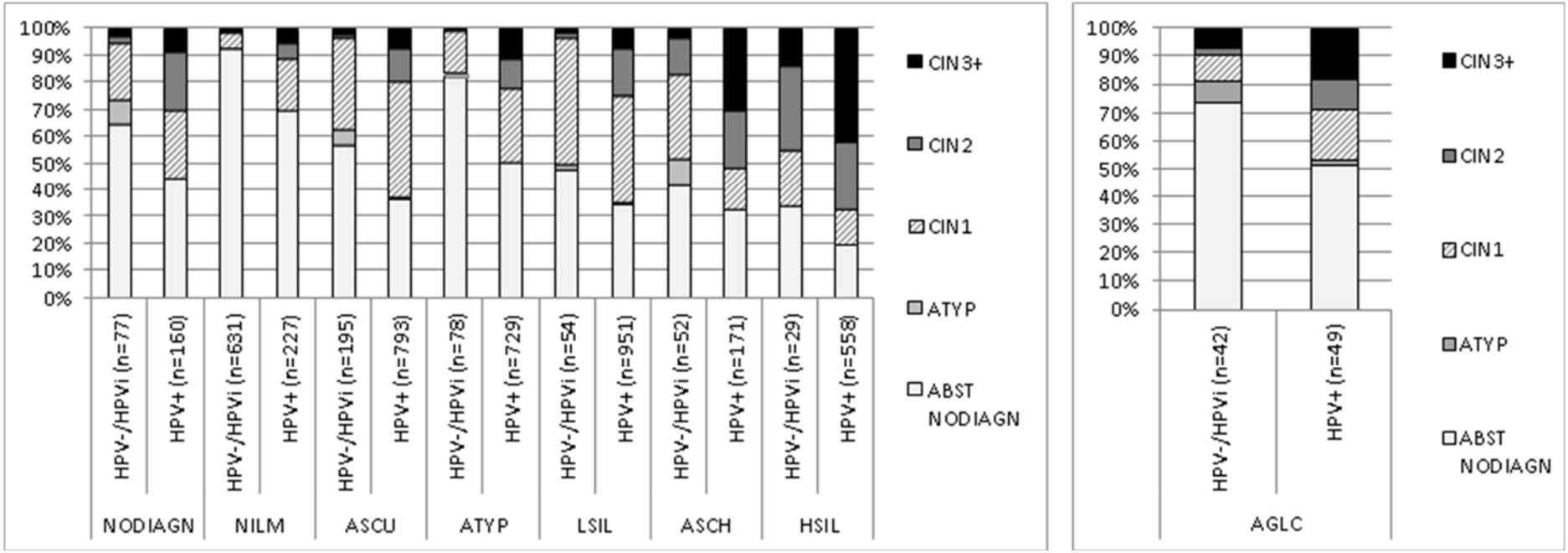
Histological diagnosis	Meaning
ABST	No dysplasia, nor tumor
ATYP	Atypical cells, not otherwise specified
CGIN	Endocervical glandular dysplasia
SQGL	Combination of CGIN with either CIN1, CIN2 or CIN3/SQIS
CIN1	Cervical intra-epithelial lesion with mild dysplasia,
CIN2	Cervical intra-epithelial lesion with moderate dysplasia,
CIN3/SQIS	Cervical intra-epithelial lesion with severe dysplasia/squamous carcinoma in situ
ADIS	Adenocarcinoma in situ
ADSQIS	Adenosquamous carcinoma in situ
SQCA	Squamous carcinoma (invasive)
ADCA	Adenocarcinoma (invasive)
ADSQCA	Adenosquamous carcinoma (invasive)
OHTMAL	In situ or invasive tumors, except squamous carcinoma, adenocarcinoma, adenosquamous carcinoma
META	Metastasis in the cervix or tumor invasion of the cervix
NODIAGN	No diagnose

For 4798 of the 12 097 cytological diagnoses of first readings that are followed with a histological diagnosis within 3 months, the result of the HPV test that is performed on the smear is known in the CHP. The cytological diagnoses are subdivided according to the HPV result (Table 114 and Figure 87).

Table 114 – Correlation between the cytological diagnosis (after first readings only), the result of the HPV test performed on the cytological sample and the first subsequent histological diagnosis within a time period of 3 months, including biopsies taken on the same day

CYTO		HISTO						
		NODIAGN	ABST	ATYP	CIN1	CIN2	CIN3+	Total
NODIAGN	HPV-/HPVi	12	38	7	16	2	2	77
	HPV+	23	48	0	41	34	14	160
NILM	HPV-/HPVi	274	308	4	34	5	6	631
	HPV+	40	119	0	42	14	12	227
ASCU	HPV-/HPVi	25	86	12	65	2	5	195
	HPV+	38	257	1	339	100	58	793
ATYP	HPV-/HPVi	27	37	1	12	1	0	78
	HPV+	65	301	0	198	84	81	729
LSIL	HPV-/HPVi	9	17	1	25	1	1	54
	HPV+	31	304	2	375	168	71	951
ASCH	HPV-/HPVi	8	14	5	16	7	2	52
	HPV+	7	50	0	26	37	51	171
HSIL	HPV-/HPVi	1	9	0	6	9	4	29
	HPV+	16	97	0	72	140	233	558
AGLC	HPV-/HPVi	3	28	3	4	1	3	42
	HPV+	8	17	1	9	5	9	49
Total		**587**	**1730**	**37**	**1280**	**610**	**552**	**4796**

Figure 87 – Correlation between the cytological diagnosis (after first readings only), the result of the HPV test performed on the cytological sample and the first subsequent histological diagnosis within a time period of 3 months, including biopsies taken on the same day



** HPV tests with an unknown result are excluded.*

Appendix 1.2. Nomenclature codes (1)

Table 115 – Number of the reimbursed medical acts for each nomenclature code (for 'SCREENING' and 'FOLLOW-UP' categories) and per year

Nomenclature code	Category	Sampling/analysis	Sample type	Hospitalized/ambulant	Year					
					2008	2009	2010	2011	2012	2013
114030	SCREENING	SAMPLING – GP	CYTO	ambulant	114 015	95 404	66 490	71 963	63 524	20 626
114041	SCREENING	SAMPLING – GP	CYTO	hospitalized	21	14	15	10	18	4
149612	SCREENING	SAMPLING - SP	CYTO	ambulant	1 146 905	897 722	605 152	742 108	651 435	197 809
149623	SCREENING	SAMPLING - SP	CYTO	hospitalized	3 405	2 843	2 326	2 203	2 192	656
588350	SCREENING	ANALYSIS - first reading	CYTO	ambulant	1 329 910	1 022 976	712 950	875 098	766 912	223 319
588361	SCREENING	ANALYSIS - first reading	CYTO	hospitalized	0	0	0	0	0	0
588873	SCREENING	ANALYSIS - second reading	CYTO	ambulant	0	12 216	27 124	33 569	31 092	8 891
588884	SCREENING	ANALYSIS - second reading	CYTO	hospitalized	0	72	155	170	155	52
114170	FOLLOW-UP	SAMPLING	CYTO	ambulant	0	2 231	6 803	7 555	6 916	2 506
114181	FOLLOW-UP	SAMPLING	CYTO	hospitalized	0	0	0	0	0	0
149634	FOLLOW-UP	SAMPLING	CYTO	ambulant	0	31 695	77 868	80 048	82 793	36 029
149645	FOLLOW-UP	SAMPLING	CYTO	hospitalized	0	52	129	145	192	62
588895	FOLLOW-UP	ANALYSIS	CYTO	ambulant	0	38 189	82 845	87 494	92 007	33 575
588906	FOLLOW-UP	ANALYSIS	CYTO	hospitalized	0	104	208	246	264	77
588932	SCREENING	ANALYSIS	HPV	ambulant	0	8 455	19 671	23 154	21 726	6 657
588943	SCREENING	ANALYSIS	HPV	hospitalized	0	33	88	75	63	28
588954	FOLLOW-UP	ANALYSIS	HPV	ambulant	0	7 640	19 440	23 158	25 652	8 958
588965	FOLLOW-UP	ANALYSIS	HPV	hospitalized	0	9	24	34	28	10

Table 116 – Number of the reimbursed medical acts for each nomenclature code (for 'COLPOSCOPY', 'FURTHER DIAGN/TREAT' and 'EXTRA' categories) and per year

Nomenclature code	Category	Hospitalized/ambulant	Year					
			2008	2009	2010	2011	2012	2013
431955	COLPOSCOPY	ambulant	359 427	326 619	278 425	280 646	269 155	51 538
431966	COLPOSCOPY	hospitalized	894	813	673	585	561	106
149052	FURTHER DIAGN/TREAT	ambulant	4 194	4 315	4 126	4 163	4 172	1 672
149063	FURTHER DIAGN/TREAT	hospitalized	39	41	43	53	37	17
431270	FURTHER DIAGN/TREAT	ambulant	5	2	4	2	6	0
431281	FURTHER DIAGN/TREAT	hospitalized	4 250	4 059	3 686	3 344	3 046	1 043
431314	FURTHER DIAGN/TREAT	ambulant	3	9	5	7	9	3
431325	FURTHER DIAGN/TREAT	hospitalized	5 177	4 806	4 514	4 308	3 958	1 501
431336	FURTHER DIAGN/TREAT	ambulant	1	3	0	0	0	0
431340	FURTHER DIAGN/TREAT	hospitalized	340	273	286	334	295	95
431351	FURTHER DIAGN/TREAT	ambulant	0	2	3	0	0	0
431362	FURTHER DIAGN/TREAT	hospitalized	729	661	650	580	603	165
431491	FURTHER DIAGN/TREAT	ambulant	1 098	1 084	1 033	990	1 028	415
431502	FURTHER DIAGN/TREAT	hospitalized	273	200	200	172	166	47
431911	FURTHER DIAGN/TREAT	ambulant	4	7	6	6	5	0
431922	FURTHER DIAGN/TREAT	hospitalized	168	144	169	147	156	57
432110	FURTHER DIAGN/TREAT	ambulant	19 207	18 819	18 718	19 270	19 237	7 583
432121	FURTHER DIAGN/TREAT	hospitalized	178	160	147	142	163	53
432154	FURTHER DIAGN/TREAT	ambulant	3	2	15	7	3	1
432165	FURTHER DIAGN/TREAT	hospitalized	17	31	30	31	40	8
432294	FURTHER DIAGN/TREAT	ambulant	7 387	7 433	7 217	7 762	7 636	2 852

432305	FURTHER DIAGN/TREAT	hospitalized	612	569	494	525	391	177
432670	FURTHER DIAGN/TREAT	ambulant	5	4	3	8	1	0
432681	FURTHER DIAGN/TREAT	hospitalized	1 999	2 019	2 076	1 888	1 951	722
432736	FURTHER DIAGN/TREAT	ambulant	2	6	2	13	41	15
432740	FURTHER DIAGN/TREAT	hospitalized	841	986	1340	1 784	2 121	915
220290	EXTRA	ambulant	26 807	26 832	25 496	24 757	23 826	8 629
220301	EXTRA	hospitalized	5 391	4 836	4 615	4303	4 119	1 419
244915	EXTRA	ambulant	0	1	0	1	0	0
244926	EXTRA	hospitalized	328	363	337	376	362	129
244930	EXTRA	ambulant	0	0	0	0	0	0
244941	EXTRA	hospitalized	262	264	253	281	263	101
431292	EXTRA	ambulant	12	0	5	3	1	1
431303	EXTRA	hospitalized	241	215	175	205	201	66
432390	EXTRA	ambulant	18 465	18 451	18 598	18 798	18 708	7 403
432401	EXTRA	hospitalized	2 178	1 998	1 898	1 785	1 838	676
432655	EXTRA	ambulant	1	6	3	1	6	0
432666	EXTRA	hospitalized	620	628	640	683	715	289

Appendix 1.3. Nomenclature codes (2)

Table 117 – Nomenclature code - and their respective meanings – that correspond to the 'COLPOSCOPY', 'FURTHER DIAGN/TREATMENT' and 'EXTRA' categories

Nomenclature code	Category	Meaning
431955-431966	COLPOSCOPY	Microscopic colposcopy possibly with sampling
149052-149063	FURTHER DIAGN/ TREATMENT	Intracervical polypectomy
431270-431281	FURTHER DIAGN/ TREATMENT	Total abdominal hysterectomy
431314-431325	FURTHER DIAGN/ TREATMENT	Total vaginal hysterectomy, including the anterior colporrhaphy and/or possibly the posterior colpoperineorrhaphy
431336-431340	FURTHER DIAGN/ TREATMENT	Radical hysterectomy (Wertheim)
431351-431362	FURTHER DIAGN/ TREATMENT	Radical hysterectomy with lymphadenectomy in the pelvis
431491-431502	FURTHER DIAGN/ TREATMENT	Amputation of the cervix and plastic surgery with leaf of the vaginal vault (Sturmdorf)
431911-431922	FURTHER DIAGN/ TREATMENT	Vaginal intervention for uterine prolapse with supravaginal amputation of cervix, suture of cardinal ligaments at the isthmus of the uterus and anterior colporraphy, possibly including the posterior colpoperineorraphy (Manchester-Fothergill operation or variant)
432110-432121	FURTHER DIAGN/ TREATMENT	Sampling with surgical pliers of a cervix piece and/or electrocoagulation
432154-432165	FURTHER DIAGN/ TREATMENT	Abdominal ablation of the remaining cervix
432294-432305	FURTHER DIAGN/ TREATMENT	Cervical conization
432670-432681	FURTHER DIAGN/ TREATMENT	Laparoscopic assisted vaginal hysterectomy, including the vaginal intervention with anatomopathological confirmation
432736-432740	FURTHER DIAGN/ TREATMENT	Total laparoscopic assisted vaginal hysterectomy with anatomopathological confirmation
220290-220301	EXTRA	Cervical curettage, curative or exploratory, possibly including expansion and sampling through endometrial biopsy
244915-244926	EXTRA	Debulking for extensive intra-abdominal tumour (II) (total hysterectomy, omentectomy, resection of peritoneal metastases, retroperitoneal exploration with lymfadenectomy)
244930-244941	EXTRA	Debulking for extensive intra-abdominal tumour (III) (total hysterectomy, colon or small intestine resection with recovery or not of the continuity, omentectomy, resection peritoneal metastases, retroperitoneal exploration with lymfadenectomy)
431292-431303	EXTRA	Subtotal hysterectomy
432390-432401	EXTRA	Diagnostical hysteroscopy with or without biopsy or cytology, with protocol
432655-432666	EXTRA	Subtotal hysterectomy with anatomopathological confirmation

Appendix 1.4. Time delays

Figure 88 – Time delay between a first reading of a screening test and either a second reading, a HPV test (performed as part of screening test), a colposcopy, or a further diagnosis/treatment

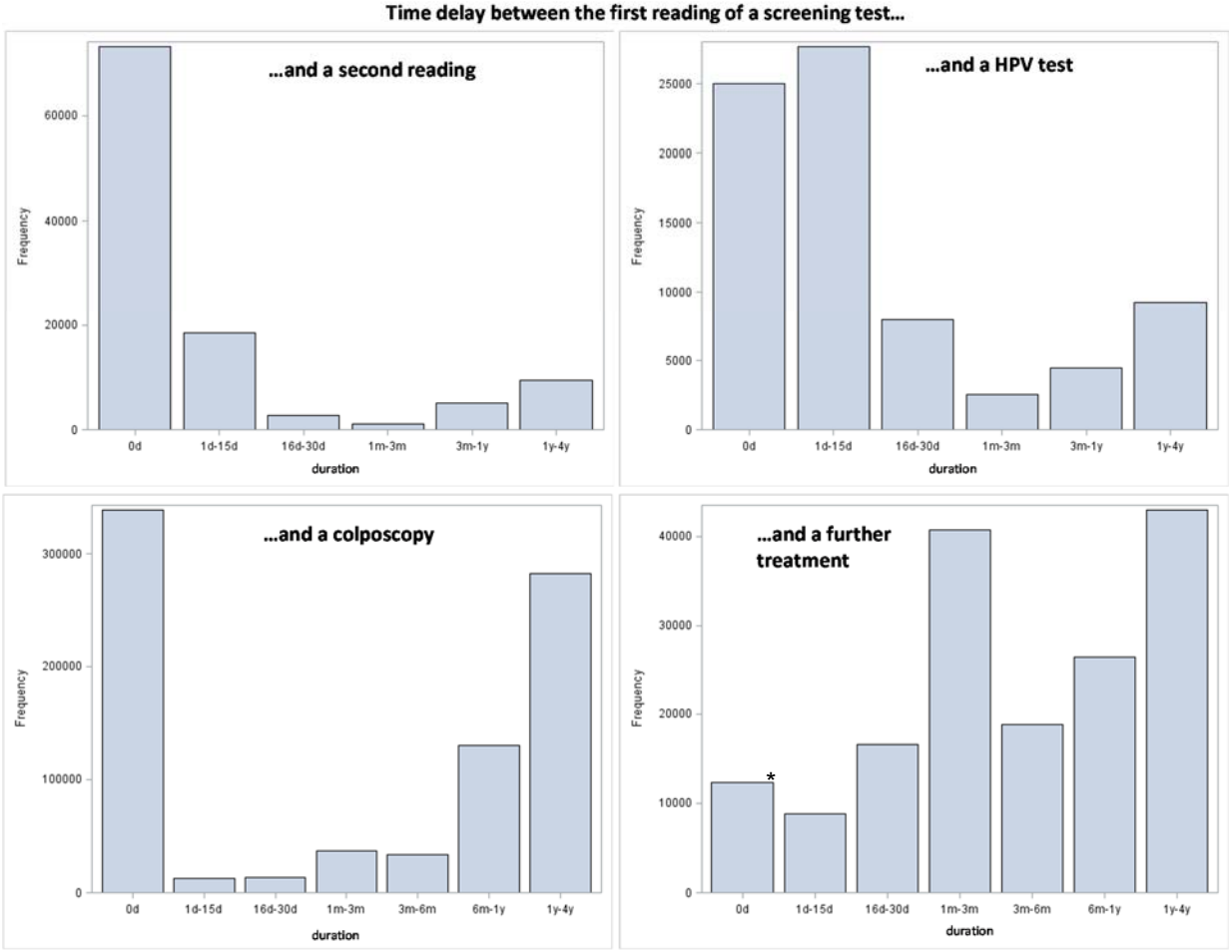


Table 118 – List of further diagnoses/treatments that have been performed on the same day than the first reading of a screening test (per nomenclature code)

Nomenclature code	Frequency
149052 *	4 873
149063	3
431270	1
431281	24
431314	1
431325	13
431340	1
431491	1
431502	1
431911	5
431922	2
432110 **	7 273
432121	19
432294	212
432305	2
432681	4
432740	5
Total	12 340

** 149052: polypectomy.*
*** 432110: biopsy.*

Figure 89 – Time delay between the sampling and the first reading of a screening test

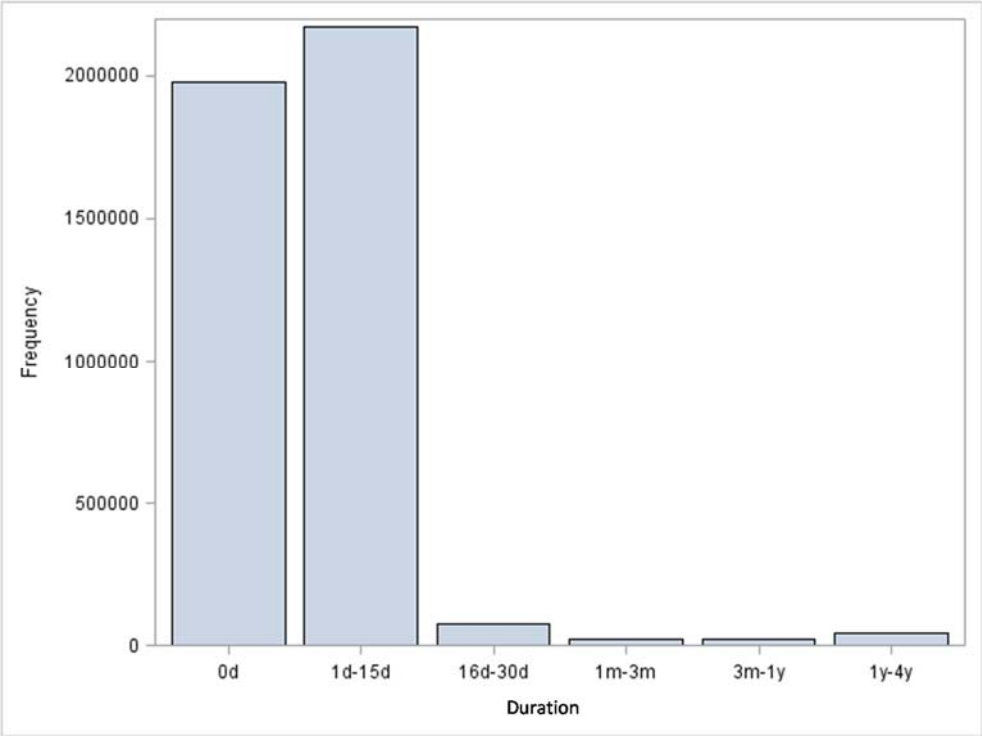


Figure 90 – Time delay between a second reading of a screening test and a HPV test (following an abnormal screening test)

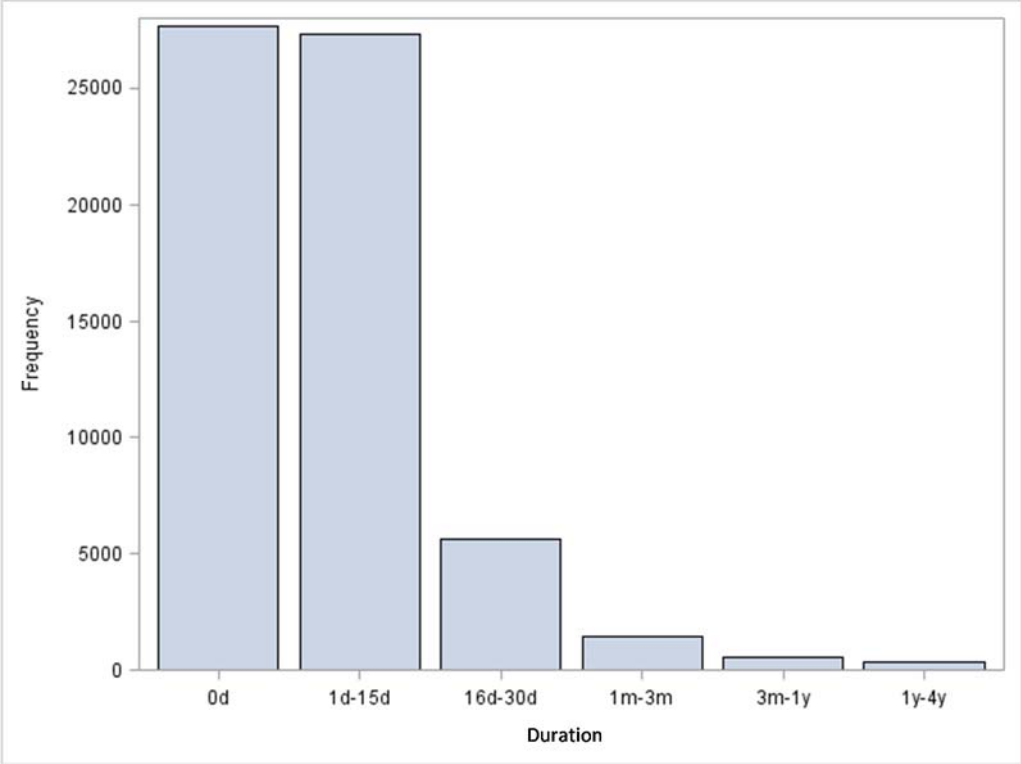
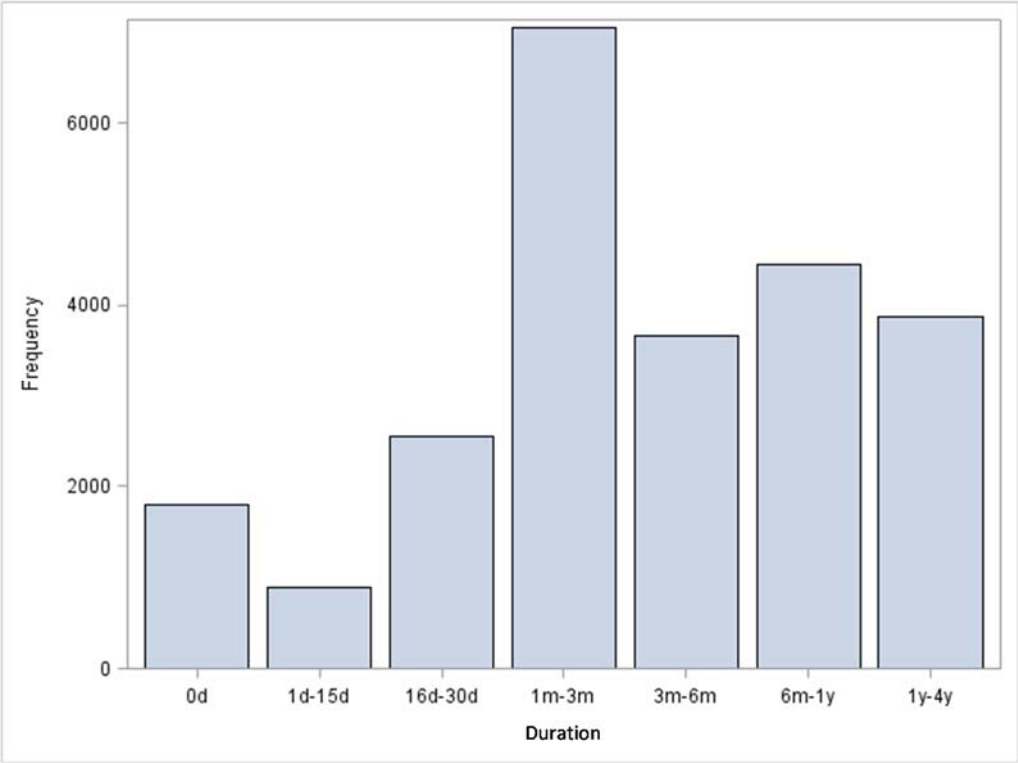


Figure 91 – Time delay between HPV test (following an abnormal screening test) and a colposcopy



Appendix 1.5. Further tables for cytological analyses

This appendix presents the results of Table 119, Table 120, Table 121, Table 122, Table 123, Table 124 for all cytological analyses registered in the CHP and the results of Tables 42 to 44 for all first readings and follow-up smears (i.e. cytological analyses in the CHP coupled to first readings and follow-up smears in IMA).

5 **Table 119 – Frequency of HPV subtypes per cytological diagnosis in the CHP (for all cytological analyses; year 2011)**

	Cytological diagnosis											
HPV genotype	NILM	ASCU	ATYP	ASCH	AGLC	HSIL	LSIL	SQGL	NODIAGN	INS/INV	OTHER	Total
1	1	1	10	0	0	0	0	0	1	0	0	**13**
5	0	0	1	0	0	0	0	0	0	0	0	**1**
6	343	18	192	0	2	28	293	0	1	0	0	**877**
7	0	0	1	0	0	0	0	0	0	0	0	**1**
8	0	0	2	0	0	0	0	0	0	0	0	**2**
11	94	6	40	2	2	6	86	0	0	0	0	**236**
13	0	0	1	0	0	0	0	0	0	0	0	**1**
16	2 329	316	1 072	50	30	489	1 499	13	61	4	1	**5 859**
18	834	118	324	13	17	102	495	8	24	1	1	**1 935**
26	1	2	0	0	0	1	0	0	0	0	0	**4**
31	1 875	120	827	21	11	174	1 065	3	23	0	0	**4 119**
32	0	0	1	0	0	0	0	0	0	0	0	**1**
33	418	44	266	13	6	101	338	5	7	0	0	**1 198**
35	439	14	183	1	2	44	225	0	7	0	0	**915**
39	1 016	64	412	3	9	99	829	4	7	0	0	**2 443**
40	0	5	1	0	0	0	1	0	0	0	0	**7**
42	18	41	1	4	0	4	13	0	4	0	0	**85**
44	0	0	1	0	0	0	0	0	0	0	0	**1**
45	289	28	124	6	3	37	179	2	15	0	0	**683**
51	931	94	470	7	5	141	993	0	17	0	0	**2 658**
52	1 038	54	647	3	12	148	817	1	19	1	0	**2 739**
53	1 555	95	506	6	11	105	1 073	1	4	0	0	**3 356**
54	17	23	0	0	0	3	4	0	0	0	0	**47**
55	5	7	1	3	0	2	4	1	1	0	0	**24**
56	937	70	377	3	5	82	845	0	13	0	0	**2 332**
58	618	53	375	6	6	108	502	0	12	0	0	**1 680**
59	914	52	323	5	5	83	578	2	11	0	0	**1 973**
61	16	17	0	4	0	1	4	1	1	0	0	**44**

62	19	28	0	1	0	8	9	1	3	0	0	**69**
66	933	60	305	2	10	69	778	2	13	0	0	**2 172**
67	28	23	3	2	1	1	9	1	3	0	0	**71**
68	185	29	85	2	3	23	216	0	3	0	1	**546**
70	10	16	2	2	0	4	4	0	2	0	0	**40**
71	2	0	0	0	0	0	0	0	0	0	0	**2**
72	2	1	0	0	0	0	0	0	1	0	0	**4**
73	14	41	0	6	0	10	12	1	1	0	0	**85**
74	0	0	1	0	0	0	0	0	0	0	0	**1**
81	11	13	0	1	0	2	1	0	0	0	0	**28**
82	2	12	0	2	0	4	4	0	0	0	0	**24**
83	10	10	0	0	0	0	3	1	0	0	0	**24**
84	18	23	0	1	0	3	4	1	0	0	0	**50**
89	20	33	0	3	0	3	8	0	1	0	0	**68**
91	0	0	1	0	0	0	0	0	0	0	0	**1**
L1	2 487	0	1 269	0	22	319	1 835	0	0	0	0	**5 932**

Table 120 – Frequency of cytological diagnoses in the CHP (for all cytological analyses) per laboratory (raw data, year 2011)

Lab	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN
Lab 1	3 970	3 081	217	16	55	159	18	10	4	-	-	-	-	-	-	-	410
Lab 2	9 367	8 674	69	1	5	470	71	17	10	-	-	-	2	-	4	2	42
Lab 3	2 796	2 725	13	1	3	35	15	2	-	-	-	-	-	-	-	-	2
Lab 4	559	501	12	44	-	-	1	-	-	-	-	-	-	-	-	-	1
Lab 5	10 794	10 191	133	10	12	324	72	3	-	-	-	-	2	-	1	1	45
Lab 6	1 427	1 327	32	8	4	23	5	5	-	-	-	-	-	1	1	-	21
Lab 7	10 621	9 248	771	1	92	341	64	21	37	-	-	-	1	-	2	-	43
Lab 8	6 123	5 446	1	163	-	6	3	-	-	-	-	-	1	-	-	-	503
Lab 9	7 959	6 787	8	287	-	160	43	6	1	-	-	-	2	-	1	1	663
Lab 10	11 546	10 673	-	547	-	177	106	6	1	1	-	-	-	-	-	-	35
Lab 11	1 219	1 079	104	-	3	11	6	3	9	-	-	-	-	-	-	-	4
Lab 12	820	733	26	35	2	10	4	9	1	-	-	-	-	-	-	-	-
Lab 13	3 604	3 267	250	4	5	30	11	7	3	-	-	-	-	-	1	1	25
Lab 14	4 260	4 003	46	1	4	147	42	2	1	-	-	-	2	-	1	-	11
Lab 15	106 494	94 492	-	4 898	-	5 827	871	262	3	-	-	-	-	1	-	-	140
Lab 16	21 096	19 297	476	2	31	664	129	28	-	-	-	-	6	8	2	3	450
Lab 17	5 898	5 520	101	247	2	10	8	9	-	-	-	-	-	-	-	1	-
Lab 18	24 312	22 555	783	13	77	385	149	19	-	-	-	-	-	1	-	-	330
Lab 19	18 713	16 378	947	-	31	1 089	169	12	9	1	-	-	2	-	1	-	74
Lab 20	17 700	69	868	17	3	560	100	12	4	-	-	-	3	1	5	-	16 058
Lab 21	20 117	10 322	285	1 101	71	29	31	273	6	-	-	-	4	1	-	16	7 978
Lab 22	15 922	15 172	202	-	51	144	57	7	-	-	-	-	-	-	-	-	289
Lab 23	4 210	3 883	42	-	5	179	62	2	-	1	-	-	1	-	-	-	35
Lab 24	8 468	7 888	79	350	4	88	17	1	1	-	-	-	3	-	3	5	29
Lab 25	5 498	5 108	-	1	-	11	52	-	-	-	-	-	-	-	1	-	325
Lab 26	5 496	4 416	466	-	38	9	21	17	8	-	-	-	1	-	-	-	520
Lab 27	6 522	3 795	32	275	1	192	6	-	-	-	-	-	1	-	-	6	2 214
Lab 28	8 552	6 172	578	-	17	416	85	20	19	-	-	-	4	1	3	-	1 237
Lab 29	7 820	7 122	246	-	31	254	46	9	4	1	-	-	1	-	3	1	102
Lab 30	15 174	13 616	741	-	232	313	93	24	11	2	-	-	2	-	4	-	136
Lab 31	4 968	4 687	174	8	16	70	3	4	-	-	-	-	-	-	-	1	5
Lab 32	5 274	5 045	126	6	22	55	5	5	3	-	-	-	1	-	2	1	3
Lab 33	11 656	10 970	371	1	33	92	54	3	4	-	-	-	2	2	2	1	121
Lab 34	7 537	5 820	867	479	1	89	37	30	25	-	-	-	2	-	1	3	183
Lab 35	7 411	6 909	273	5	11	167	18	7	-	-	-	-	2	-	3	-	16
Lab 36	2 689	2 484	97	1	6	61	25	4	3	-	-	-	1	-	-	-	7
Lab 37	3 019	2 816	81	4	-	85	27	4	2	-	-	-	-	-	-	-	-
Lab 38	2 426	2 180	168	4	1	12	11	31	6	-	-	-	-	-	3	1	9
Lab 39	10 541	9 540	310	-	147	196	308	11	-	-	-	-	-	-	-	14	15
Lab 40	12 426	11 712	354	59	1	43	31	25	194	-	-	-	-	-	-	-	7

Lab 41	15 772	13 757	1 402	-	33	407	77	28	56	-	1	-	1	1	2	-	7
Lab 42	5 458	5 179	167	3	24	33	31	7	5	-	-	-	-	-	-	-	9
Lab 43	4 685	4 362	131	-	22	97	54	1	1	-	-	-	5	-	1	-	11
Lab 44	15 510	14 985	106	48	11	149	41	4	-	-	-	-	-	-	-	-	166
Lab 45	18 861	18 381	284	-	22	121	38	1	1	-	-	-	-	1	1	-	11
Lab 46	3 989	3 744	141	-	4	57	3	3	3	1	-	-	1	-	-	-	32
Lab 47	8 107	7 670	107	2	9	142	43	4	2	-	-	-	3	-	3	-	122
Lab 48	5 202	4 195	764	-	21	113	42	47	5	-	-	-	-	-	1	-	14
Lab 49	5 693	5 037	64	-	1	95	27	6	-	-	-	-	-	-	-	-	463
Lab 50	7 150	6 962	50	-	8	59	43	1	-	-	-	-	-	-	-	-	27
Lab 51	2 204	1 963	35	100	12	29	9	4	1	-	-	-	1	-	-	-	50
Lab 52	6 899	6 643	40	1	1	96	80	5	-	-	-	-	1	-	-	-	32
Lab 53	13 500	12 452	440	1	20	401	90	25	24	-	-	-	4	1	4	-	38
Lab 54	21 047	18 116	2 189	-	215	9	90	97	-	-	-	-	-	-	-	-	331
Lab 55	27 975	13 445	524	6 463	82	1 199	175	594	36	1	-	-	13	2	4	4	5 433
Lab 56	2 665	2 573	60	3	1	19	4	2	-	1	-	-	-	-	-	-	2
Lab 57	4 986	4 795	98	-	15	54	11	5	1	-	-	-	1	-	3	-	3
Lab 58	14 540	10 609	727	52	1	308	97	29	-	-	-	-	5	-	6	-	2 706
Lab 59	9 531	8 314	341	9	10	442	83	105	6	-	-	-	4	-	3	-	214
Lab 60	9 997	9 245	140	8	13	344	57	34	1	-	-	-	4	-	6	-	145
Lab 61	6 407	5 176	350	-	12	540	123	18	9	-	-	1	2	-	-	-	176
Lab 62	3 504	3 257	155	-	13	34	18	9	-	-	-	-	-	-	-	-	18
Total	**648 686**	**546 563**	**18 664**	**15 279**	**1 567**	**17 681**	**4 112**	**1 939**	**520**	**9**	**1**	**1**	**91**	**21**	**78**	**62**	**42 098**
Maximum	**106 494**	**94 492**	**2 189**	**6 463**	**232**	**5 827**	**871**	**594**	**194**	**2**	**1**	**1**	**13**	**8**	**6**	**16**	**16 058**
3rd quartile	**12 233.5**	**10 537.25**	**366.75**	**30.5**	**23.5**	**311.75**	**79.25**	**20.75**	**5.75**	**0**	**0**	**0**	**2**	**0**	**2**	**1**	**270.25**
Median	**7 280.5**	**5 996**	**148**	**2.5**	**10.5**	**105**	**42**	**7**	**1**	**0**	**0**	**0**	**1**	**0**	**0.5**	**0**	**40**
1st quartile	**4 366.25**	**3 817**	**61**	**0**	**2**	**34.25**	**15.5**	**3.25**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**11**
Minimum	**559**	**69**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Table 121 – Frequency of cytological diagnosis in the CHP (for all cytological analyses, as percentages, year 2011), the method used to analyze cervical smears and the use of an automated system, per laboratory

Laboratory	TOTAL	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	ADIS	ADSQCA	ADSQIS	SQCA	META	ADCA	OTHMAL	NODIAGN	Liquid based (LB) or conventional (CON)	Imaging system used
Lab 1	100.0%	77.6%	5.5%	0.4%	1.4%	4.0%	0.5%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	10.3%	LB	HTI
Lab 2	100.0%	92.6%	0.7%	0.0%	0.1%	5.0%	0.8%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	LB	No
Lab 3	100.0%	97.5%	0.5%	0.0%	0.1%	1.3%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	No
Lab 4	100.0%	89.6%	2.1%	7.9%	0.0%	0.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	Unknown	Unkown
Lab 5	100.0%	94.4%	1.2%	0.1%	0.1%	3.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	LB	No
Lab 6	100.0%	93.0%	2.2%	0.6%	0.3%	1.6%	0.4%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	1.5%	LB	No
Lab 7	100.0%	87.1%	7.3%	0.0%	0.9%	3.2%	0.6%	0.2%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	LB	HTI
Lab 8	100.0%	88.9%	0.0%	2.7%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.2%	LB	No
Lab 9	100.0%	85.3%	0.1%	3.6%	0.0%	2.0%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.3%	LB	No
Lab 10	100.0%	92.4%	0.0%	4.7%	0.0%	1.5%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	Unknown	No
Lab 11	100.0%	88.5%	8.5%	0.0%	0.2%	0.9%	0.5%	0.2%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	Unknown	No
Lab 12	100.0%	89.4%	3.2%	4.3%	0.2%	1.2%	0.5%	1.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Unknown	No
Lab 13	100.0%	90.6%	6.9%	0.1%	0.1%	0.8%	0.3%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	Unknown	No
Lab 14	100.0%	94.0%	1.1%	0.0%	0.1%	3.5%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	No
Lab 15	100.0%	88.7%	0.0%	4.6%	0.0%	5.5%	0.8%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	Unknown	HTI
Lab 16	100.0%	91.5%	2.3%	0.0%	0.1%	3.1%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	LB	HTI
Lab 17	100.0%	93.6%	1.7%	4.2%	0.0%	0.2%	0.1%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	LB	Unkown
Lab 18	100.0%	92.8%	3.2%	0.1%	0.3%	1.6%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%	LB (50%) + CON (50%)	Unkown
Lab 19	100.0%	87.5%	5.1%	0.0%	0.2%	5.8%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Unknown	HTI
Lab 20	100.0%	0.4%	4.9%	0.1%	0.0%	3.2%	0.6%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	90.7%	LB (95%) + CON (5%)	HTI
Lab 21	100.0%	51.3%	1.4%	5.5%	0.4%	0.1%	0.2%	1.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	39.7%	LB (99%) + CON (1%)	No
Lab 22	100.0%	95.3%	1.3%	0.0%	0.3%	0.9%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.8%	LB (x%) + CON (x%)	No
Lab 23	100.0%	92.2%	1.0%	0.0%	0.1%	4.3%	1.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	LB	HTI
Lab 24	100.0%	93.2%	0.9%	4.1%	0.0%	1.0%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.3%	LB (95%) + CON (5%)	Unkown

Lab 25	100.0%	92.9%	0.0%	0.0%	0.0%	0.2%	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.9%	LB (95%) + CON(5%)	No
Lab 26	100.0%	80.3%	8.5%	0.0%	0.7%	0.2%	0.4%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	9.5%	Unknown	Unkown
Lab 27	100.0%	58.2%	0.5%	4.2%	0.0%	2.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	33.9%	CON	No
Lab 28	100.0%	72.2%	6.8%	0.0%	0.2%	4.9%	1.0%	0.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	14.5%	LB	No
Lab 29	100.0%	91.1%	3.1%	0.0%	0.4%	3.2%	0.6%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.3%	LB	HTI
Lab 30	100.0%	89.7%	4.9%	0.0%	1.5%	2.1%	0.6%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	LB	HTI
Lab 31	100.0%	94.3%	3.5%	0.2%	0.3%	1.4%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	No
Lab 32	100.0%	95.7%	2.4%	0.1%	0.4%	1.0%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	No
Lab 33	100.0%	94.1%	3.2%	0.0%	0.3%	0.8%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	LB	HTI
Lab 34	100.0%	77.2%	11.5%	6.4%	0.0%	1.2%	0.5%	0.4%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.4%	LB	Unkown
Lab 35	100.0%	93.2%	3.7%	0.1%	0.1%	2.3%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB	Unkown
Lab 36	100.0%	92.4%	3.6%	0.0%	0.2%	2.3%	0.9%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	No
Lab 37	100.0%	93.3%	2.7%	0.1%	0.0%	2.8%	0.9%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	Unknown	No
Lab 38	100.0%	89.9%	6.9%	0.2%	0.0%	0.5%	0.5%	1.3%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.4%	LB	No
Lab 39	100.0%	90.5%	2.9%	0.0%	1.4%	1.9%	2.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	Unknown	Unkown
Lab 40	100.0%	94.3%	2.8%	0.5%	0.0%	0.3%	0.2%	0.2%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	Unknown	Unkown
Lab 41	100.0%	87.2%	8.9%	0.0%	0.2%	2.6%	0.5%	0.2%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	LB	No
Lab 42	100.0%	94.9%	3.1%	0.1%	0.4%	0.6%	0.6%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	LB (x%) + CON (x%)	No
Lab 43	100.0%	93.1%	2.8%	0.0%	0.5%	2.1%	1.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.2%	LB	Unkown
Lab 44	100.0%	96.6%	0.7%	0.3%	0.1%	1.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%	LB (x%) + CON (x%)	HTI
Lab 45	100.0%	97.5%	1.5%	0.0%	0.1%	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	LB	BD FocalPoint™ Slide Profiler
Lab 46	100.0%	93.9%	3.5%	0.0%	0.1%	1.4%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	LB	No
Lab 47	100.0%	94.6%	1.3%	0.0%	0.1%	1.8%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	LB	No
Lab 48	100.0%	80.6%	14.7%	0.0%	0.4%	2.2%	0.8%	0.9%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	No
Lab 49	100.0%	88.5%	1.1%	0.0%	0.0%	1.7%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.1%	Unknown	Unkown
Lab 50	100.0%	97.4%	0.7%	0.0%	0.1%	0.8%	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	Unknown	Unkown
Lab 51	100.0%	89.1%	1.6%	4.5%	0.5%	1.3%	0.4%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.3%	CON	No
Lab 52	100.0%	96.3%	0.6%	0.0%	0.0%	1.4%	1.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	Unknown	Unkown
Lab 53	100.0%	92.2%	3.3%	0.0%	0.1%	3.0%	0.7%	0.2%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	LB	No
Lab 54	100.0%	86.1%	10.4%	0.0%	1.0%	0.0%	0.4%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%	LB (x%) + CON (x%)	No
Lab 55	100.0%	48.1%	1.9%	23.1%	0.3%	4.3%	0.6%	2.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	19.4%	LB	Unkown

Lab 56	100.0%	96.5%	2.3%	0.1%	0.0%	0.7%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	Unknown	No
Lab 57	100.0%	96.2%	2.0%	0.0%	0.3%	1.1%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.1%	Unknown	Unkown
Lab 58	100.0%	73.0%	5.0%	0.4%	0.0%	2.1%	0.7%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	18.6%	LB	No
Lab 59	100.0%	87.2%	3.6%	0.1%	0.1%	4.6%	0.9%	1.1%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.2%	Unknown	No
Lab 60	100.0%	92.5%	1.4%	0.1%	0.1%	3.4%	0.6%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	1.5%	Unknown	No
Lab 61	100.0%	80.8%	5.5%	0.0%	0.2%	8.4%	1.9%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.7%	LB	Unkown
Lab 62	100.0%	93.0%	4.4%	0.0%	0.4%	1.0%	0.5%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	Unknown	No
Total	100.0%	84.3%	2.9%	2.4%	0.2%	2.7%	0.6%	0.3%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	6.5%		
Max	97.%	14.69 %	23.10 %	1.53%	8.43%	2.92%	2.12%	1.56%	0.04%	0.01%	0.02%	0.11%	0.07%	0.12%	0.13%	90.72 %	Max		
3rd quartile	93.94%	4.77%	0.39%	0.32%	2.99%	0.74%	0.24%	0.09%	0.00%	0.00%	0.00%	0.03%	0.00%	0.03%	0.01%	2.22%	3rd quartile		
Median	92.23%	2.74%	0.05%	0.14%	1.60%	0.53%	0.12%	0.02%	0.00%	0.00%	0.00%	0.01%	0.00%	0.00%	0.00%	0.49%	Median		
1st quartile	87.30%	1.24%	0.00%	0.04%	0.90%	0.32%	0.06%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.22%	1st quartile		
Min	0.39%	0.00%	0.00%	0.00%	0.00%	0.05%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	Min		

HTI: Hologic, ThinPrep Imager

Table 122 – Number of HPV tests performed after a cytology (first reading or follow-up) according to the IMA data and / or CHP, number of HPV tests registered in the CHP per laboratory (raw numbers and as percentages, year 2011). For each laboratory is indicated which laboratory performs the HPV test and which test is used

	HPV performed after cytology (30days) according to IMA data and / or CHP								HPV performed after cytology (30days) and registered in CHP		Which laboratory performs the HPV tests?	Which test is used for HPV detection?	
	Raw numbers				Percentages				Raw numbers	Percentages			
Laboratory (1)	HPV from CHP only (2)	HPV from IMA only (3)	HPV from CHP AND IMA (4)	TOTAL HPV (from CHP and/or IMA) (5)	HPV from CHP only (6)	HPV from IMA only (7)	HPV from CHP AND IMA (8)	TOTAL HPV (from CHP and/or IMA) (9)	TOTAL HPV from CHP (10)	TOTAL HPV from CHP (/TIOTAL HPV from CHP and IMA) (11)	(12)	Firm (13)	Type of HPV test used (14)
Lab 1	185	12	408	605	30.6%	2.0%	67.4%	100.0%	593	98.0%	Ohter pathology lab	Roche	Linear array HPV genotyping test
Lab 2	119	4	15	138	86.2%	2.9%	10.9%	100.0%	134	97.1%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 3	21	1	11	33	63.6%	3.0%	33.3%	100.0%	32	97.0%	Clinical lab	Qiagen	digene HC2 HR HPV DNA test
Lab 4	5	-	-	5	100.0%	0.0%	0.0%	100.0%	5	100.0%	Unknown	Unknown	Unknown
Lab 5	1	93	7	101	1.0%	92.1%	6.9%	100.0%	8	7.9%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 6	62	-	-	62	100.0%	0.0%	0.0%	100.0%	62	100.0%	Ohter pathology lab	Unknown	Unknown
Lab 7	243	1	797	1041	23.3%	0.1%	76.6%	100.0%	1040	99.9%	Unknown	Qiagen bioMérieux for positive samples	digene HC2 HR HPV DNA test NucliSENS EasyQ HPV
Lab 8	130	1	-	131	99.2%	0.8%	0.0%	100.0%	130	99.2%	Pathology lab itself	Unknown	Unknown
Lab 9	249	-	1	250	99.6%	0.0%	0.4%	100.0%	250	100.0%	Ohter pathology lab	Roche	Linear array HPV genotyping test
Lab 10	99	9	442	550	18.0%	1.6%	80.4%	100.0%	541	98.4%	Unknown	Unknown	Unknown
Lab 11	10	13	51	74	13.5%	17.6%	68.9%	100.0%	61	82.4%	Unknown	Unknown	Unknown
Lab 12	-	32	2	34	0.0%	94.1%	5.9%	100.0%	2	5.9%	Unknown	Unknown	Unknown
Lab 13	40	13	248	301	13.3%	4.3%	82.4%	100.0%	288	95.7%	Unknown	Unknown	Unknown

Lab 14	34	-	22	56	60.7%	0.0%	39.3%	100.0%	56	100.0%	Clinical lab own hospital	Qiagen	digene HC2 HPV DNA test
Lab 15	96 712	3	9224	105 939	91.3%	0.0%	8.7%	100.0%	105 936	100.0%	Pathology lab itself	AML	AML probe
Lab 16	73	-	506	579	12.6%	0.0%	87.4%	100.0%	579	100.0%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 17	99	-	-	99	100.0%	0.0%	0.0%	100.0%	99	100.0%	Pathology lab itself	DAKO	Immuno histochemistry
Lab 18	215	51	627	893	24.1%	5.7%	70.2%	100.0%	842	94.3%	Pathology lab itself	Hologic	Cervista HPV HR
Lab 19	328	50	1,003	1,381	23.8%	3.6%	72.6%	100.0%	1,331	96.4%	Ohter pathology lab	Roche	Cobas
Lab 20	194	3	229	426	45.5%	0.7%	53.8%	100.0%	423	99.3%	Pathology lab itself	Roche	Cobas
Lab 21	618	3	108	729	84.8%	0.4%	14.8%	100.0%	726	99.6%	Clinical lab own hospital	Abbott	Abbot RealTime HR HPV
Lab 22	41	115	6	162	25.3%	71.0%	3.7%	100.0%	47	29.0%	Ohter pathology lab	Hologic	Cervista HPV HR
Lab 23	15	1	54	70	21.4%	1.4%	77.1%	100.0%	69	98.6%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 24	288	34	409	731	39.4%	4.7%	56.0%	100.0%	697	95.3%	Ohter pathology lab	Abbott AML	Abbot RealTime HR HPV AML probe
Lab 25	-	279	-	279	0.0%	100.0 %	0.0%	100.0%	-	0.0%	Ohter pathology lab	Qiagen	digene HC2 HPV DNA test
Lab 26	27	3	60	90	30.0%	3.3%	66.7%	100.0%	87	96.7%	Unknown	Unknown	Unknown
Lab 27	204	61	50	315	64.8%	19.4%	15.9%	100.0%	254	80.6%	Clinical lab	Abbott	Abbot RealTime HR HPV
Lab 28	1424	-	869	2293	62.1%	0.0%	37.9%	100.0%	2293	100.0%	Pathology lab itself	Hologic	Cervista HPV HR
Lab 29	121	12	337	470	25.7%	2.6%	71.7%	100.0%	458	97.4%	Ohter pathology lab	Roche	Linear array HPV genotyping test
Lab 30	242	1	918	1,161	20.8%	0.1%	79.1%	100.0%	1,160	99.9%	Pathology lab itself	Roche	Amplicor
Lab 31	27	19	145	191	14.1%	9.9%	75.9%	100.0%	172	90.1%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 32	13	2	136	151	8.6%	1.3%	90.1%	100.0%	149	98.7%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 33	162	5	807	974	16.6%	0.5%	82.9%	100.0%	969	99.5%	Pathology lab itself	Roche	Linear array HPV genotyping test
Lab 34	80	459	945	1,484	5.4%	30.9%	63.7%	100.0%	1,025	69.1%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 35	23	7	256	286	8.0%	2.4%	89.5%	100.0%	279	97.6%	Clinical lab own hospital	Qiagen	digene HC2 HPV DNA test

Lab 36	103	2	104	209	49.3%	1.0%	49.8%	100.0%	207	99.0%	Clinical lab own hospital	Greiner Bio One	PapilloCheck
Lab 37	138	-	79	217	63.6%	0.0%	36.4%	100.0%	217	100.0%	Unknown	Unknown	Unknown
Lab 38	41	19	101	161	25.5%	11.8%	62.7%	100.0%	142	88.2%	Clinical lab	Roche	Cobas
Lab 39	13	423	203	639	2.0%	66.2%	31.8%	100.0%	216	33.8%	Unknown	Unknown	Unknown
Lab 40	24	406	203	633	3.8%	64.1%	32.1%	100.0%	227	35.9%	Clinical lab own hospital	Roche	Cobas
Lab 41	151	11	1581	1743	8.7%	0.6%	90.7%	100.0%	1,732	99.4%	Clinical lab own hospital	Abbott Microgen Bioproducts	Abbot RealTime HR HPV INNO-LiPA HPV genotypering
Lab 42	61	5	92	158	38.6%	3.2%	58.2%	100.0%	153	96.8%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 43	74	2	149	225	32.9%	0.9%	66.2%	100.0%	223	99.1%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 44	78	70	92	240	32.5%	29.2%	38.3%	100.0%	170	70.8%	Pathology lab itself	Roche	Linear array HPV genotyping test
Lab 45	165	2	423	590	28.0%	0.3%	71.7%	100.0%	588	99.7%	Clinical lab own hospital	Qiagen	digene HC2 HPV DNA test
Lab 46	19	16	3	38	50.0%	42.1%	7.9%	100.0%	22	57.9%	Clinical lab	Roche	Amplicor
Lab 47	22	-	72	94	23.4%	0.0%	76.6%	100.0%	94	100.0%	Ohter pathology lab	AML	AML probe
Lab 48	101	43	535	679	14.9%	6.3%	78.8%	100.0%	636	93.7%	Clinical lab	Qiagen	digene HC2 HPV DNA test
Lab 49	51	32	23	106	48.1%	30.2%	21.7%	100.0%	74	69.8%	Unknown	Unknown	Unknown
Lab 50	2	3	1	6	33.3%	50.0%	16.7%	100.0%	3	50.0%	Unknown	Unknown	Unknown
Lab 51	8	6	7	21	38.1%	28.6%	33.3%	100.0%	15	71.4%	Ohter pathology lab	Roche	Cobas
Lab 52	88	-	39	127	69.3%	0.0%	30.7%	100.0%	127	100.0%	Unknown	Unknown	Unknown
Lab 53	747	-	9	756	98.8%	0.0%	1.2%	100.0%	756	100.0%	Ohter pathology lab	Qiagen	digene HC2 HPV DNA test
Lab 54	205	25	394	624	32.9%	4.0%	63.1%	100.0%	599	96.0%	Clinical lab own hospital	bioMérieux	NucliSENS EasyQ HPV
Lab 55	1638	3	4695	6336	25.9%	0.0%	74.1%	100.0%	6,333	100.0%	Pathology lab itself	Qiagen	digene HC2 HPV DNA test
Lab 56	7	35	22	64	10.9%	54.7%	34.4%	100.0%	29	45.3%	Clinical lab own hospital	Unknown	Unknown
Lab 57	56	1	113	170	32.9%	0.6%	66.5%	100.0%	169	99.4%	Unknown	Unknown	Unknown

Lab 58	113	207	682	1,002	11.3%	20.7%	68.1%	100.0%	795	79.3%	Clinical lab own hospital	Unknown	Unknown
Lab 59	143	13	319	475	30.1%	2.7%	67.2%	100.0%	462	97.3%	Clinical lab own hospital	Unknown	Unknown
Lab 60	20	48	129	197	10.2%	24.4%	65.5%	100.0%	149	75.6%	Clinical lab own hospital	Unknown	Unknown
Lab 61	43	3	377	423	10.2%	0.7%	89.1%	100.0%	420	99.3%	Ohter pathology lab	Unknown	Unknown
Lab 62	51	68	45	164	31.1%	41.5%	27.4%	100.0%	96	58.5%	Unknown	bioMérieux	NucliSENS EasyQ HPV
Total	**106 266**	**2730**	**29 185**	**138 181**	**76.9%**	**2.0%**	**21.1%**	**100.0%**	**135 451**	**98.0%**			

Table 123 – Overview table of ASCU / ATYP diagnoses (after first reading or follow-up, columns 2-6), HPV tests registered in CHP and / or IMA (columns 7-8), HPV tests performed on ASCU/ATYP (columns 9-12) and HPV positive ASCU / ATYP (columns 13-16) (raw numbers and as percentages, year 2011)

	ASCU / ATYP diagnoses					HPV tests registered		HPV tests performed on ASCU/ATYP				HPV positive ASCU / ATYP			
Laboratory (1)	TOTAL CYTO (from CHP) (2)	ASCU (3)	ATYP (4)	ASCU + ATYP (5)	% ASCU+ATYP (/TOTAL CYTO) (6)	TOTAL HPV (CHP and/or IMA) (7)	% TOTAL HPV (/TOTAL CYTO) (8)	TOTAL HPV (CHP and/or IMA) after ASCU (9)	TOTAL HPV (CHP and/or IMA) after ATYP (10)	TOTAL HPV (CHP and/or IMA) after ASCU or ATYP (11)	% TOTAL HPV after ASCU or ATYP (/TOTAL ASCU+ATYP) (12)	HPV+ from CHP after ASCU (13)	HPV+ from CHP after ATYP (14)	TOTAL HPV+ from CHP after ASCU or ATYP (15)	% TOTAL HPV+ after HPV on ASCU or ATYP HPV (/TOTAL ASCU+ATYP) on
Lab 1	3 970	217	16	233	5.87%	605	15.24%	105	16	121	51.93%	61	2	63	52.07%
Lab 2	9 367	69	1	70	0.75%	138	1.47%	52	-	52	74.29%	33	-	33	63.46%
Lab 3	2 796	13	1	14	0.50%	33	1.18%	11	-	11	78.57%	4	-	4	36.36%
Lab 4	559	12	44	56	10.02%	5	0.89%	2	2	4	7.14%	-	2	2	50.00%
Lab 5	10 794	133	10	143	1.32%	101	0.94%	48	-	48	33.57%	2	-	2	* 4.17%
Lab 6	1 427	32	8	40	2.80%	62	4.34%	29	7	36	90.00%	16	2	18	50.00%
Lab 7	10 621	771	1	772	7.27%	1 041	9.80%	617	-	617	79.92%	156	-	156	25.28%
Lab 8	6 123	1	163	164	2.68%	131	2.14%	1	107	108	65.85%	1	69	70	64.81%
Lab 9	7 959	8	287	295	3.71%	250	3.14%	6	176	182	61.69%	4	87	91	50.00%
Lab 10	11 546	-	547	547	4.74%	550	4.76%	-	516	516	94.33%	-	217	217	42.05%
Lab 11	1 219	104	-	104	8.53%	74	6.07%	55	-	55	52.88%	17	-	17	30.91%
Lab 12	820	26	35	61	7.44%	34	4.15%	21	2	23	37.70%	1	-	1	* 4.35%
Lab 13	3 604	250	4	254	7.05%	301	8.35%	195	1	196	77.17%	89	1	90	45.92%
Lab 14	4 260	46	1	47	1.10%	56	1.31%	36	1	37	78.72%	24	-	24	64.86%
Lab 15	106 494	-	4 898	4 898	4.60%	105 939	99.48%	-	4 895	4 895	99.94%	-	3 807	3 807	77.77%
Lab 16	21 096	476	2	478	2.27%	579	2.74%	468	2	470	98.33%	149	1	150	31.91%
Lab 17	5 898	101	247	348	5.90%	99	1.68%	32	21	53	15.23%	11	6	17	32.08%
Lab 18	24 312	783	13	796	3.27%	893	3.67%	399	2	401	50.38%	156	1	157	39.15%
Lab 19	18 713	947	-	947	5.06%	1 381	7.38%	736	-	736	77.72%	198	-	198	26.90%
Lab 20	17 700	868	17	885	5.00%	426	2.41%	283	1	284	32.09%	130	1	131	46.13%
Lab 21	20 117	285	1 101	1 386	6.89%	729	3.62%	255	51	306	22.08%	102	32	134	43.79%

Lab 22	15 922	202	-	202	1.27%	162	1.02%	95	-	95	47.03%	4	-	4	* 4.21%
Lab 23	4 210	42	-	42	1.00%	70	1.66%	40	-	40	95.24%	19	-	19	47.50%
Lab 24	8 468	79	350	429	5.07%	731	8.63%	54	171	225	52.45%	30	106	136	60.44%
Lab 25	5 498	-	1	1	0.02%	279	5.07%	-	1	1	100.0%	-	-	-	* 0.00%
Lab 26	5 496	466	-	466	8.48%	90	1.64%	32	-	32	6.87%	13	-	13	40.63%
Lab 27	6 522	32	275	307	4.71%	315	4.83%	6	47	53	17.26%	-	15	15	28.30%
Lab 28	8 552	578	-	578	6.76%	2 293	26.81%	514	-	514	88.93%	169	-	169	32.88%
Lab 29	7 820	246	-	246	3.15%	470	6.01%	202	-	202	82.11%	102	-	102	50.50%
Lab 30	15 174	741	-	741	4.88%	1 161	7.65%	720	-	720	97.17%	297	-	297	41.25%
Lab 31	4 968	174	8	182	3.66%	191	3.84%	169	1	170	93.41%	83	1	84	49.41%
Lab 32	5 274	126	6	132	2.50%	151	2.86%	124	-	124	93.94%	67	-	67	54.03%
Lab 33	11 656	371	1	372	3.19%	974	8.36%	369	-	369	99.19%	211	-	211	57.18%
Lab 34	7 537	867	479	1 346	17.86%	1 484	19.69%	859	410	1 269	94.28%	259	-	259	20.41%
Lab 35	7 411	273	5	278	3.75%	286	3.86%	267	-	267	96.04%	109	-	109	40.82%
Lab 36	2 689	97	1	98	3.64%	209	7.77%	93	-	93	94.90%	35	-	35	37.63%
Lab 37	3 019	81	4	85	2.82%	217	7.19%	76	4	80	94.12%	36	2	38	47.50%
Lab 38	2 426	168	4	172	7.09%	161	6.64%	108	-	108	62.79%	23	-	23	21.30%
Lab 39	10 541	310	-	310	2.94%	639	6.06%	272	-	272	87.74%	39	-	39	* 14.34%
Lab 40	12 426	354	59	413	3.32%	633	5.09%	295	54	349	84.50%	33	10	43	* 12.32%
Lab 41	15 772	1 402	-	1 402	8.89%	1 743	11.05%	1 088	-	1 088	77.60%	321	-	321	29.50%
Lab 42	5 458	167	3	170	3.11%	158	2.89%	46	-	46	27.06%	26	-	26	56.52%
Lab 43	4 685	131	-	131	2.80%	225	4.80%	112	-	112	85.50%	55	-	55	49.11%
Lab 44	15 510	106	48	154	0.99%	240	1.55%	64	12	76	49.35%	28	6	34	44.74%
Lab 45	18 861	284	-	284	1.51%	590	3.13%	275	-	275	96.83%	224	-	224	81.45%
Lab 46	3 989	141	-	141	3.53%	38	0.95%	26	-	26	18.44%	3	-	3	* 11.54%
Lab 47	8 107	107	2	109	1.34%	94	1.16%	66	-	66	60.55%	21	-	21	31.82%
Lab 48	5 202	764	-	764	14.69%	679	13.05%	565	-	565	73.95%	114	-	114	20.18%
Lab 49	5 693	64	-	64	1.12%	106	1.86%	47	-	47	73.44%	18	-	18	38.30%
Lab 50	7 150	50	-	50	0.70%	6	0.08%	2	-	2	4.00%	1	-	1	* 50.00%
Lab 51	2 204	35	100	135	6.13%	21	0.95%	1	-	1	0.74%	-	-	-	** 0.00%
Lab 52	6 899	40	1	41	0.59%	127	1.84%	10	-	10	24.39%	5	-	5	50.00%
Lab 53	13 500	440	1	441	3.27%	756	5.60%	414	-	414	93.88%	200	-	200	48.31%
Lab 54	21 047	2 189	-	2 189	10.40%	624	2.96%	549	-	549	25.08%	176	-	176	32.06%
Lab 55	27 975	524	6 463	6 987	24.98%	6 336	22.65%	453	198	651	9.32%	247	82	329	50.54%
Lab 56	2 665	60	3	63	2.36%	64	2.40%	37	-	37	58.73%	9	-	9	* 24.32%
Lab 57	4 986	98	-	98	1.97%	170	3.41%	88	-	88	89.80%	49	-	49	55.68%
Lab 58	14 540	727	52	779	5.36%	1 002	6.89%	613	44	657	84.34%	205	22	227	34.55%
Lab 59	9 531	341	9	350	3.67%	475	4.98%	304	5	309	88.29%	57	-	57	18.45%

Lab 60	9 997	140	8	148	1.48%	197	1.97%	111	5	116	78.38%	26	-	26	22.41%
Lab 61	6 407	350	-	350	5.46%	423	6.60%	206	-	206	58.86%	43	-	43	20.87%
Lab 62	3 504	155	-	155	4.42%	164	4.68%	112	-	112	72.26%	19	-	19	* 16.96%
Total	**648 686**	**18 664**	**15 279**	**33 943**	**5.23%**	**138 181**	**21.30%**	**12 835**	**6 752**	**19 587**	**57.71%**	**4 530**	**4 472**	**9 002**	**45.96%**

Table 124 – Correlation between cytological diagnosis in the CHP (after all cytological analyses) and the first subsequent histological diagnosis within a time delay of between 0 day and 3 months

	HISTO														
CYTO	**ABST / NODIAGN**	**ATYP**	**CIN1**	**CIN2**	**SQIS**	**CGIN**	**SQGL**	**ADIS**	**ADSQIS**	**SQCA**	**ADCA**	**ADSQCA**	**OTHMAL**	**META**	**Total**
NILM / NODIAGN	4 483	77	301	133	105	-	1	3	-	15	21	2	5	10	5 156
ASCU / ATYP	1 380	102	928	289	245	1	-	2	-	15	5	-	1	2	2 970
ASCH	146	14	72	79	87	-	-	1	-	7	1	-	1	1	409
LSIL	848	31	1 100	410	157	-	-	3	-	4	1	-	-	-	2 554
HSIL	389	23	297	593	874	3	3	9	-	49	6	1	-	1	2 248
AGLC	119	6	21	9	10	1	-	3	-	2	9	-	-	3	183
SQGL	36	1	23	17	18	-	1	2	-	5	-	-	1	-	104
IN SITU / INVASIVE	18	-	1	5	17	-	-	5	1	49	27	2	4	3	132
Total	7 419	254	2 743	1 535	1 513	5	5	28	1	146	70	5	12	20	13 756

(*) Exclusive HSIL.

APPENDIX 2. GENERAL TERMS OF REFERENCE FOR REFERENCE CENTERS FOR HUMAN MICROBIOLOGY

The general terms for Belgian Reference Centres are listed in the following 13 criteria. This criteria should be completed with specific criteria for human papillomaviruses as defined in subchapter 4. Legal regulations are published in Royal Decree of 9February 2001, published on 01/03/2011 in Staatsblad/Moniteur belge, pp 14133- 14138. (http://www.coseas.be/files/energy/Arrete_01-03-2011.pdf).

This document describes the criteria and activities a reference center must fulfill. These criteria form the basis of the knowledge and experience the centers must have both before their application and during the agreement. More specific criteria per pathogen are listed in the specific terms of reference.

Candidates are expected to have the following capacities:

1. To possess scientific expertise and experience in the pathology or the pathogen, and to be able to demonstrate this on the basis of scientific publications.
2. To be able to communicate the test results in a timely manner (as specified by the candidate laboratory in the application file) to the client and to be able to do this in two national languages (Dutch and French) depending on the language spoken by the client.
3. To provide technical support to recognized laboratories:
   - o by establishing the guidelines regarding the conditions (epidemiological, clinical and microbiological) of the sample analysis and of the sample transportation (sampling procedure, transport conditions, contact person, turn around time, how and when the results will be sent);
   - o by supplying sampling and shipping material, if necessary;
   - o by informing them about relevant new techniques.
4. To follow innovations in the field of the specific pathogen and to contribute to the validation and development of new techniques in diagnosis and typing.
5. To coordinate the used methods and to develop their standardization.
6. To determine the precise characteristics of the pathogen.
7. To have proof of the implementation of quality requirements.

The final aim is accreditation under ISO15189 for the reference activities. A transitory period is accepted for the selected laboratories that are not yet accredited; they must have BELAC ISO15189 accreditation two years after their official selection.

At the moment of applying, the applicant must either be accredited under ISO17025 or ISO15189, or to be recognized according to the quality criteria of the AR/KB of 3/12/1999, or to hold the position of a reference laboratory in the current IPH sentinel laboratory network. If the laboratory is not accredited, it must be able to prove its quality control.

8. To participate in the investigation of grouped cases and epidemics (strain typing, comparison of strains isolated from patients and other sources).
9. To provide the required information and expertise to contribute to an appropriate reaction in case of an emergency, an outbreak or another health threat.
10. To develop and manage a network of recognized laboratories in collaboration with the IPH, and to encourage these laboratories to send strains and samples for analysis in order to have a good geographical representativeness.
11. To participate in the surveillance of the pathogen (or group of pathogens) and communicating, with the support of the IPH, the following information to the competent authorities:
    - o epidemiological information: date of birth, sex, address (postal code), date and type of sample, isolated or grouped cases, nosocomial origin;
    - o the results of the analysis;
    - o if indicated, the antimicrobial sensitivity profile, the vaccination status of the patient, the source of infection.
12. To participate in the early warning system organized by the competent public health authorities in order to detect unusual events by reporting:
    - o an increase in pathogen frequency.

or antimicrobial resistance, the presence of clusters of cases:

- o case(s) of a rare disease;
- o the identification of a new pathogen type, the occurrence of new clinical forms or the increased virulence of a known pathogen;
- o information related to similar problems in foreign countries;
- o the occurrence of unusual antimicrobial resistance profiles;
- o the detection of unusual nosocomial infections.

13. To participate in the dissemination of scientific results: publications, communication during scientific meetings.
14. To produce an annual scientific and financial report.
15. To participate in existing international surveillance networks and in international research projects.

APPENDIX 3. COST IMPLICATIONS - SENSITIVITY ANALYSES

Appendix 3.1. Cost parameters

	Cost HPV analysis		
	€58.29	**€20.00**	**€11.00**
Total number of cancers HPV screening	222	222	222
Total number of cancers cytology screening	462	462	462
Difference	240	240	240
Deaths attributable to cervix cancer HPV screening	82	82	82
Deaths attributable to cervix cancer cytology screening	178	178	178
Difference	95	95	95
Total life years HPV screening	5340240	5340240	5340240
Total life years cylology screening	5337361	5337361	5337361
Difference	2878	2878	2878
Total life years HPV screening (discounted)	3660369	3660369	3660369
Total life years cylology screening (discounted)	3658751	3658751	3658751
Difference	1618	1618	1618
Total cost HPV screening	€ 88 773 717	€ 54 915 027	€ 46 956 599
Total cost cylology screening	€ 83 773 482	€ 82 611 714	€ 82 338 642
Difference	€ 5 000 235	-€ 27 696 687	-€ 35 382 043
Total cost HPV screening (discounted)	€ 59 215 279	€ 37 495 861	€ 32 390 748
Total cost cylology screening (discounted)	€ 52 228 722	€ 51 502 024	€ 51 331 215
Difference	€ 6 986 557	-€ 14 006 163	-€ 18 940 467

ICER not reported because HPV dominant, except for an assumed cost for a HPV test of €58.29 for which the ICER is €4319 per year of life gained.

Appendix 3.2. Parameters related to Cytology screening

	ASCUS positive		Proportion ASCUS that is positive after retest		HPV + among tested for triage	
	Low 0.02	High 0.06	Low 0.40	High 0.80	Low 0.20	High 0.60
Total number of cancers HPV screening	222	222	222	222	222	222
Total number of cancers cytology screening	462	462	462	462	462	462
Difference	240	240	240	240	240	240
Deaths attributable to cervix cancer HPV screening	82	82	82	82	82	82
Deaths attributable to cervix cancer cytology screening	178	178	178	178	178	178
Difference	95	95	95	95	95	95
Total life years HPV screening	5340240	5340240	5340240	5340240	5340240	5340240
Total life years cylology screening	5337361	5337361	5337361	5337361	5337361	5337361
Difference	2878	2878	2878	2878	2878	2878
Total life years HPV screening (discounted)	3660369	3660369	3660369	3660369	3660369	3660369
Total life years cylology screening (discounted)	3658751	3658751	3658751	3658751	3658751	3658751
Difference	1618	1618	1618	1618	1618	1618
Total cost HPV screening	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074
Total cost cylology screening	€ 80 267 543	€ 85 866 123	€ 81 861 087	€ 84 272 580	€ 82 259 585	€ 84 053 470
Difference	-€ 12 088 470	-€ 17 687 050	-€ 13 682 013	-€ 16 093 507	-€ 14 080 512	-€ 15 874 396
Total cost HPV screening (discounted)	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382
Total cost cylology screening (discounted)	€ 50 046 220	€ 53 527 192	€ 51 039 498	€ 52 533 914	€ 51 291 711	€ 52 391 700
Difference	-€ 4 041 838	-€ 7 522 810	-€ 5 035 117	-€ 6 529 532	-€ 5 287 329	-€ 6 387 318

	Higher grade than ASCUS		Proportion CIN1 per screening round		Proportion CIN2 per screening round	
	Low 0.2	High 0.6	Low 0.002	High 0.006	Low 0.001	High 0.006
Total number of cancers HPV screening	222	222	222	222	222	222
Total number of cancers cytology screening	462	462	462	462	462	462
Difference	240	240	240	240	240	240
Deaths attributable to cervix cancer HPV screening	82	82	82	82	82	82
Deaths attributable to cervix cancer cytology screening	178	178	178	178	178	178
Difference	95	95	95	95	95	95
Total life years HPV screening	5340240	5340240	5340240	5340240	5340240	5340240
Total life years cylology screening	5337361	5337361	5337361	5337361	5337361	5337361

Difference	2878	2878	2878	2878	2878	2878
Total life years HPV screening (discounted)	3660369	3660369	3660369	3660369	3660369	3660369
Total life years cylology screening (discounted)	3658751	3658751	3658751	3658751	3658751	3658751
Difference	1618	1618	1618	1618	1618	1618
Total cost HPV screening	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074
Total cost cylology screening	€ 81 385 067	€ 88 859 584	€ 81 956 908	€ 83 445 795	€ 82 740 370	€ 84 334 186
Difference	-€ 13 205 993	-€ 20 680 511	-€ 13 777 835	-€ 15 266 722	-€ 14 561 296	-€ 16 155 112
Total cost HPV screening (discounted)	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382
Total cost cylology screening (discounted)	€ 50 755 466	€ 55 338 754	€ 51 092 436	€ 52 023 751	€ 51 578 383	€ 52 586 844
Difference	-€ 4 751 084	-€ 9 334 373	-€ 5 088 054	-€ 6 019 369	-€ 5 574 001	-€ 6 582 463

	Proportion CIN3 per screening round		**biopsy/colposcopy**	
	Low 0.001	**High** 0.006	**Low** 0.2	**High** 0.8
Total number of cancers HPV screening	222	222	222	222
Total number of cancers cytology screening	462	462	462	462
Difference	240	240	240	240
Deaths attributable to cervix cancer HPV screening	82	82	82	82
Deaths attributable to cervix cancer cytology screening	178	178	178	178
Difference	95	95	95	95
Total life years HPV screening	5340240	5340240	5340240	5340240
Total life years cylology screening	5337361	5337361	5337361	5337361
Difference	2878	2878	2878	2878
Total life years HPV screening (discounted)	3660369	3660369	3660369	3660369
Total life years cylology screening (discounted)	3658751	3658751	3658751	3658751
Difference	1618	1618	1618	1618
Total cost HPV screening	€ 68 179 074	€ 68 179 074	€ 68 179 074	€ 68 179 074
Total cost cylology screening	€ 82 162 711	€ 84 748 960	€ 82 140 419	€ 83 993 248
Difference	-€ 13 983 638	-€ 16 569 886	-€ 13 961 345	-€ 15 814 174
Total cost HPV screening (discounted)	€ 46 004 382	€ 46 004 382	€ 46 004 382	€ 46 004 382
Total cost cylology screening (discounted)	€ 51 217 143	€ 52 846 382	€ 51 207 224	€ 52 366 188
Difference	-€ 5 212 762	-€ 6 842 000	-€ 5 202 842	-€ 6 361 806

Appendix 3.3. Parameters related to HPV screening

	Proportion cytology triage + biopsy/colposcopy				Proportion CIN1 per screening round	
	0.4	0.6	0.2	0.8	0.0058	0.0125
Total number of cancers HPV screening	222	222	222	222	222	222
Total number of cancers cytology screening	462	462	462	462	462	462
Difference	240	240	240	240	240	240
Deaths attributable to cervix cancer HPV screening	82	82	82	82	82	82
Deaths attributable to cervix cancer cytology screening	178	178	178	178	178	178
Difference	95	95	95	95	95	95
Total life years HPV screening	5340240	5340240	5340240	5340240	5340240	5340240
Total life years cylology screening	5337361	5337361	5337361	5337361	5337361	5337361
Difference	2878	2878	2878	2878	2878	2878
Total life years HPV screening (discounted)	3660369	3660369	3660369	3660369	3660369	3660369
Total life years cylology screening (discounted)	3658751	3658751	3658751	3658751	3658751	3658751
Difference	1618	1618	1618	1618	1618	1618
Total cost HPV screening	€ 68 032 399	€ 68 258 052	€ 67 320 004	€ 69 038 144	€ 67 608 350	€ 69 130 279
Total cost cylology screening	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 83 066 833
Difference	-€ 15 034 435	-€ 14 808 781	-€ 15 746 830	-€ 14 028 690	-€ 15 458 483	-€ 13 936 554
Total cost HPV screening (discounted)	€ 45 789 857	€ 46 119 895	€ 45 427 025	€ 46 581 738	€ 45 641 215	€ 46 609 659
Total cost cylology screening (discounted)	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 786 706
Difference	-€ 5 996 849	-€ 5 666 811	-€ 6 359 681	-€ 5 204 968	-€ 6 145 491	-€ 5 177 047

	Proportion CIN2 per screening round		Proportion CIN3 per screening round		effect HPV op invasive		proportion hr HPV persisting after one year	
	0.00464649	0.00836369	0.00389291	0.00549588	0.3	0.8	0.3	0.7
Total number of cancers HPV screening	222	222	222	222	156	374	222	222
Total number of cancers cytology screening	462	462	462	462	462	462	462	462
Difference	240	240	240	240	305	87	240	240
Deaths attributable to cervix cancer HPV screening	82	82	82	82	58	139	82	82
Deaths attributable to cervix cancer cytology screening	178	178	178	178	178	178	178	178
Difference	95	95	95	95	120	39	95	95
Total life years HPV screening	5340240	5340240	5340240	5340240	5341025	5338408	5340240	5340240
Total life years cylology screening	5337361	5337361	5337361	5337361	5337361	5337361	5337361	5337361

Difference	2878	2878	2878	2878	3663	1047	2878	2878
Total life years HPV screening (discounted)	3660369	3660369	3660369	3660369	3660810	3659339	3660369	3660369
Total life years cylology screening (discounted)	3658751	3658751	3658751	3658751	3658751	3658751	3658751	3658751
Difference	1618	1618	1618	1618	2059	588	1618	1618
Total cost HPV screening	€ 68 298 764	€ 67 979 590	€ 68 238 061	€ 68 100 424	€ 67 446 284	€ 69 888 915	€ 66 803 085	€ 69 860 838
Total cost cylology screening	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 83 066 833	€ 82 766 584	€ 83 367 083
Difference	-€ 14 768 069	-€ 15 087 244	-€ 14 828 772	-€ 14 966 410	-€ 15 620 549	-€ 13 177 918	-€ 15 963 499	-€ 13 506 245
Total cost HPV screening (discounted)	€ 45 809 547	€ 46 329 106	€ 45 875 346	€ 46 176 430	€ 45 577 793	€ 46 999 756	€ 45 093 705	€ 47 114 114
Total cost cylology screening (discounted)	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 786 706	€ 51 609 678	€ 51 963 734
Difference	-€ 5 977 159	-€ 5 457 600	-€ 5 911 360	-€ 5 610 276	-€ 6 208 913	-€ 4 786 950	-€ 6 515 973	-€ 4 849 620

Appendix 3.4. Common parameters

As we are comparing 2 cohorts where each women is either screened with HPV as primary test or with cytology screening, these parameters only influence the adjustment we had to make to the Belgian BCR data as explained in the main text.

	effectiveness (RR screened/unscreened)		Coverage Cervical screening	
	0.4	0.6	0.35	0.8
Total number of cancers HPV screening	194	259	282	178
Total number of cancers cytology screening	404	538	587	371
Difference	210	280	305	193
Deaths attributable to cervix cancer HPV screening	72	96	105	66
Deaths attributable to cervix cancer cytology screening	155	207	226	143
Difference	83	111	121	77
Total life years HPV screening	5340595	5339766	5339465	5340799
Total life years cylology screening	5338076	5336408	5335802	5338486
Difference	2519	3358	3663	2312
Total life years HPV screening (discounted)	3660573	3660096	3659922	3660690
Total life years cylology screening (discounted)	3659158	3658209	3657863	3659391
Difference	1416	1887	2059	1300
Total cost HPV screening	€ 67 868 978	€ 68 592 535	€ 68 855 646	€ 67 691 054
Total cost cylology screening	€ 82 411 391	€ 83 940 756	€ 84 496 889	€ 82 035 318
Difference	-€ 14 542 414	-€ 15 348 221	-€ 15 641 242	-€ 14 344 264
Total cost HPV screening (discounted)	€ 45 809 860	€ 46 263 744	€ 46 428 792	€ 45 698 250
Total cost cylology screening (discounted)	€ 51 391 492	€ 52 313 658	€ 52 648 992	€ 51 164 729
Difference	-€ 5 581 631	-€ 6 049 915	-€ 6 220 200	-€ 5 466 480

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