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Review Article

HPV-based cervical screening: Rationale, expectations and future perspectives of the new Dutch screening programme

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ABSTRACT

Based on scientific data showing that HPV testing provides better protection against cervical precancer and cancer than cytology, in 2011 the Dutch Health Council advised the Minister of Welfare, Health and Sports to replace cytology by HPV testing in the Dutch population-based screening programme. After a successful evaluation of the feasibility of HPV-based screening in 2014, primary HPV testing for cervical screening was implemented in 2017. The Netherlands has been one of the first countries worldwide to implement nationwide HPV-based screening and its experience with the new programme is therefore followed with great interest. In this manuscript, we present an overview of the studies that were instrumental in the choice of HPV assay and triage strategy, the adjustment of screening starting and exit ages and intervals, and the implementation of HPV self-sampling. Finally, we review the cost-effectiveness of the proposed new screening algorithm and we explore future perspectives. The rationale behind the new Dutch HPV-based screening programme, which is based on risk management, could serve as a guidance to other countries that are planning to implement HPV-based screening in the near future.

1. Introduction

Since the lead time between cervical intraepithelial neoplasia (CIN) to cervical cancer is relatively long, and since CIN lesions can be detected and treated effectively, cervical cancer is a preventable disease (Vink et al., 2013). Cervical screening programmes aim to detect and treat cervical precancer in order to prevent the development of cervical cancer. Several countries, including Australia and New Zealand, the Nordic countries, the United Kingdom, Italy, and the Netherlands, have nationwide or regionally organized cervical screening programmes (Wentzensen et al., 2017). In the Netherlands, regional screening was established in the early seventies and nationwide organized screening was implemented in 1994 (Hanselaar, 1995).

Since the introduction of cervical screening in the seventies, screening programmes have been based on cytomorphological evaluation of cells exfoliated from the cervical surface (i.e. cervical cytology) (Papanicolaou, 1942). However, cervical cytology has two main limitations as a primary screening test: its moderate sensitivity (50–70%) for detection of high-grade CIN and its limited reproducibility due to its subjective character (Kitchener et al., 2006; Nanda et al., 2000). Even in countries with adequate cytology quality assurance systems these limitations remain of great influence on the performance of screening programmes (Stoler and Schiffman, 2001; Massad et al., 2013; Jordan et al., 2008). Nevertheless, cytology-based screening programmes have been effective in decreasing cervical cancer mortality and incidence by 50–80% as compared to the pre-screening era (Kitchener et al., 2006; Arbyn et al., 2009; van der Aa et al., 2008; Sasieni et al., 2003; Peto et al., 2004; Landy et al., 2016).

In recent years, the decrease in cervical cancer incidence seems to have levelled off (de Kok et al., 2011; Baldur-Felskov et al., 2015; Cervantes-Amat et al., 2015; Smith et al., 2017). This indicates that the maximum impact of cytology-based screening programmes has been reached. Consequently, a change regarding the primary screening test was needed to facilitate further reduction in cervical cancer incidence. Persistent infection with high-risk human papillomavirus (HPV) is the main cause for cervical cancer development, and this knowledge has given rise to the development of HPV assays for use in cervical screening (zur Hausen, 2002; Schiffman et al., 2007; Walboomers et al., 1999; Munoz et al., 2006). Clinical studies have evaluated the use of HPV testing for cervical screening. Four European randomised trials

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Table 1
Requirements for HPV assays in primary cervical screening.

1	Clinical sensitivity for CIN2+ of ≥90% as compared to the comparator assay[a]
2	Clinical specificity for CIN2+ of ≥98% as compared to the comparator assay[a]
3	Intra- and inter-laboratory reproducibility with a lower confidence bound ≥87%

Adapted from Meijer et al. Int J Cancer, 2009.
CIN2+ = CIN2 or worse.
[a] Comparator assay = HC2 or GP5+/6+ PCR EIA.

(Swedescreen, POBASCAM, ARTISTIC and NTCC) showed that HPV testing significantly reduced the detection of cervical precancer and cancer (CIN3+) at the second screen with 47–66% as compared to conventional cytology (Naucler et al., 2007; Bulkmans et al., 2007a; Rijkaart et al., 2012a; Kitchener et al., 2009; Ronco et al., 2010). Based on these data and data from North-American countries (Mayrand et al., 2007; Sherman et al., 2003), in 2011 the Dutch Health Council advised the Ministry of Health to replace cytology by HPV testing for cervical screening (Dutch Health Council, 2011).

Most HPV infections clear spontaneously. Only a small proportion of HPV infections persist and, eventually, may develop into CIN3+ (Schiffman et al., 2007; Bulkmans et al., 2007b). Adjunct triage testing of HPV-positive women is required to identify women with clinically relevant cervical disease. Various strategies have been proposed for triage of HPV-positive women. The clinical performance of these strategies varies between studies and currently there is no consensus on the optimal management of HPV-positive women (Dijkstra et al., 2014; Rijkaart et al., 2012b; Castle et al., 2011; Wright Jr. et al., 2011; Naucler et al., 2009; Ronco et al., 2016). In addition to establishing the most suitable triage strategy, decisions about the HPV assay, adjustment of screening starting and exit ages and intervals, and the implementation of HPV self-sampling have to be made prior to the implementation of HPV-based screening, and finally, a cost-effectiveness evaluation of the proposed new screening algorithms should be conducted.

The Netherlands is one of the first countries worldwide to implement nationwide HPV-based screening, and its experience with the new programme is therefore followed with great interest. In this manuscript we shortly discuss the organisational structure of the new Dutch cervical screening programme and the scientific evidence that contributed to the design of the programme.

2. Organisation of screening in the Netherlands

The Ministry of Health (MOH) provides the budget for screening and delegates the implementation of a screening programme to the National Institute of Public Health and Environment (RIVM). The RIVM directs and monitors the implementation of screening, while the regional screening organisations are responsible for the practical execution of the screening programme.

The Dutch Health Council advises the MOH about major changes regarding screening. The Dutch Health Council is an independent organisation in which experts of the field are appointed. If the Health Council issues a positive advice regarding a new development, the MOH takes the final decision whether to implement the new development or not. If it is decided that the development should be implemented, the RIVM is responsible for implementation and monitoring. To obtain support from health care professionals, the RIVM appoints a programme committee with representatives of the associations of professionals (e.g. general practitioners, pathologists, gynaecologists, technicians, etc.) that advises the RIVM and the regional screening organisations on the practical organisation and implementation of the new screening programme.

3. HPV assays suitable for use in HPV-based cervical screening

HPV assays should have an optimal balance between clinical sensitivity and specificity for detection of CIN3+ (Bulkmans et al., 2007b; Castle et al., 2015). An HPV assay with limited sensitivity may fail to detect clinically relevant HPV infections, while the use of a very sensitive HPV assay will have limited clinical specificity, causing unnecessary referrals and excessive follow-up of test-positive women. In the four European randomised clinical trials (Swedescreen, POBASCAM, ARTISTIC and NTCC) that demonstrated efficacy of HPV-testing, the GP5+/6+ PCR enzyme immunoassay (EIA) and the Hybrid Capture-2 (HC2) assays were used (Naucler et al., 2007; Bulkmans et al., 2007a; Rijkaart et al., 2012a; Kitchener et al., 2009; Ronco et al., 2010). Consequently, an international team of experts formulated equivalence criteria in which data from these trials were used to set a standard for test performance and characteristics (Table 1) (Meijer et al., 2009). Only assays that have been proven to fulfil these criteria can be considered as clinically validated and can be used for cervical screening purposes.

In 2015, a systematic review was conducted in which seven HPV assays were identified to fully match the equivalence criteria: HC2 (Qiagen, Gaithersburg, MD, USA), GP5+/6+ PCR-EIA (Labo Biomedical Products B·V., Rijswijk, The Netherlands), Abbott RT hrHPV test (Abbott, Wiesbaden, Germany), cobas 4800 HPV test (Roche Molecular System, Pleasanton, CF, USA), PapilloCheck HPV-Screening test (Greiner Bio-One, Frickenhausen, Germany), BD Onclarity HPV assay (BD Diagnostics, Sparks, MD, USA) and HPV-Risk assay (Self-Screen B.V., Amsterdam, The Netherlands) (Arbyn et al., 2015; Poljak et al., 2016). Accordingly, these assays are considered to be acceptable for use in HPV-based cervical screening. After a tendering procedure in which several assays were compared with respect to performance, quality and price criteria, a five year contract was awarded to Roche for the use of the cobas 4800 HPV test as the primary test in the Dutch cervical screening programme (Table 2).

4. Strategies for triage of HPV-positive women

4.1. Triage strategy requirements

Various strategies have been proposed for triage of HPV-positive women, but currently there is no consensus on the optimal management of HPV-positive women. A triage strategy should balance safety, in terms of CIN3+ detection, and screening-related burden, in terms of colposcopy referrals. The most optimal balance may differ from country to country, depending on locally accepted risks and available resources (Meijer and Berkhof, 2012).

In studies evaluating the clinical performance of triage strategies, safety and screening-related burden are represented by the negative predictive value (NPV) and the positive predictive value (PPV), respectively. NPV and PPV thresholds are used to evaluate the acceptability of triage strategies. As referral of women for colposcopy is done on the basis of short-term CIN3+ risks, thresholds are based on results from cross-sectional studies with two to three year follow-up results.

An accepted safety threshold is a minimal CIN3+ NPV of 98%, which translates into a maximum CIN3+ risk of 2% within the subsequent two to three years (Dijkstra et al., 2014; Rijkaart et al., 2012b;

Table 2
Overview of the changes regarding the previous, cytology-based and the new, HPV-based screening programme in the Netherlands.

	Previous cervical screening programme (until December 2016)	New cervical screening programme (started January 2017)
Primary screening test	Cytology on cervical scrape	HPV test on cervical scrape
Triage test	In case of BMD cytology: repeat cytology (and optional HPV test) after 6 and 18 months	In case of HPV-positive test result: cytology and repeat cytology after 6 months
First screen	At age 30	At age 30
Last screen	At age 60	-At age 60; -If HPV-positive at age 60: repeat at age 65
Screening intervals	5 years	-5 years -If HPV-negative at age 40 or 50: interval 10 years
Self-sampling	n/a	Self-sampling for non-responders on request
Estimated cervical cancer incidence and mortality	Incidence: ~700 Mortality: ~210	Incidence: ~600 Mortality:~175
Estimated costs	~€45 million per year	-~€50 million per year in the first five years after implementation; -~€40 million per year after the first five years

BMD = borderline or mild dyskaryosis; n/a = not applicable.

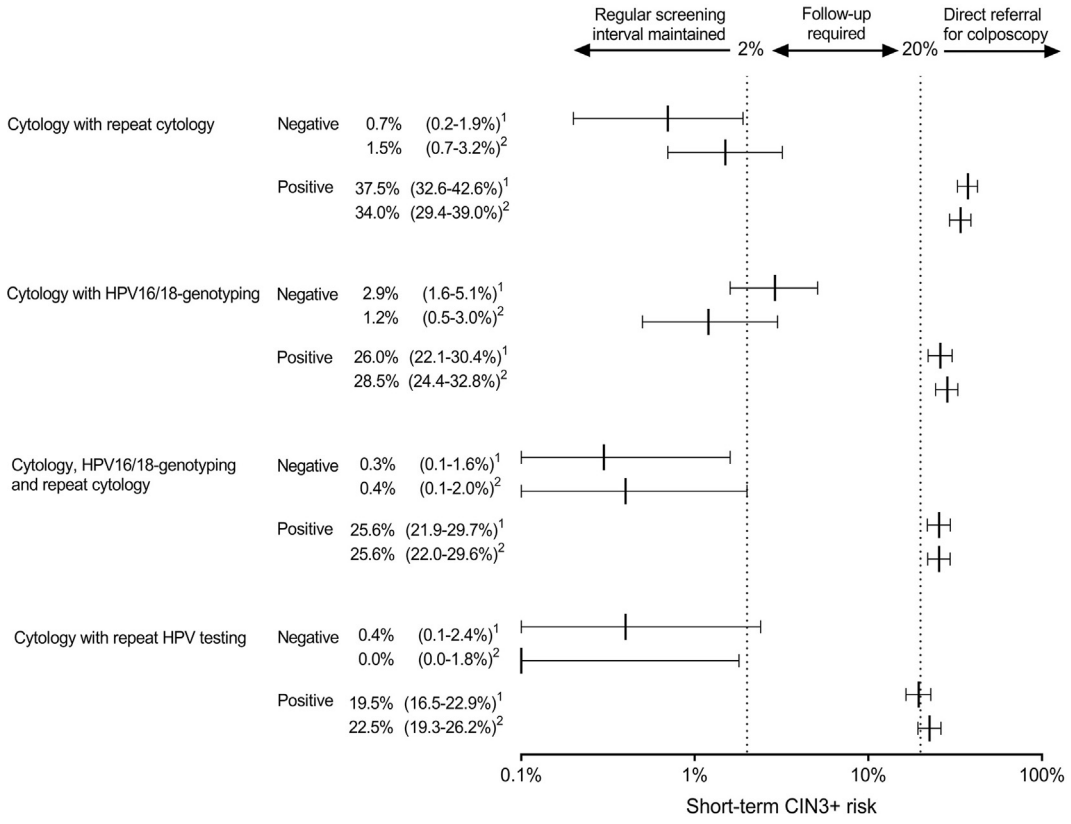

Fig. 1. Overview of the short-term CIN3+ risk estimates of various triage strategies within the post-hoc analyses performed in the VUSA-Screen and POBASCAM cohorts.
Legends:
Adapted from [1]VUSA-Screen cohort (Rijkaart et al., 2012a, 2012b, 2012c); [2]POBASCAM cohort (Dijkstra et al., 2014).
CIN3+ = cervical intraepithelial neoplasia grade 3 or worse.

Castle et al., 2008). This NPV threshold is based on the CIN3+ risk among women with borderline or mild dyskaryosis (BMD) cytology (comparable to atypical squamous cells of undetermined significance (ASC-US) or low grade squamous intraepithelial lesion (LSIL) in the Bethesda classification) at baseline and normal cytology at 6 and 18 months follow-up. In the previous Dutch cytology-based screening programme, these women had a CIN3+ risk of 1.2% and were referred back to routine screening (Rijkaart et al., 2012c; Solomon et al., 2002). Consequently, a short-term CIN3+ risk threshold of 2% was used, indicating that regular five-yearly screening intervals could be maintained for women with a CIN3+ risk of 2% or lower (Fig. 1).

The PPV of a triage strategy greatly impacts colposcopy referral rates and the associated costs. Within the USA, women with a short-term CIN3+ risk, or equivalently, a PPV of 10% or higher are directly referred for colposcopy. Within the Netherlands, a minimal CIN3+ PPV of 20% has been used based on the PPV of ~20% in the previous cytology based screening programme. This means that only women with a short-term CIN3+ risk of 20% or higher are directly referred for colposcopy (Fig. 1) (Dijkstra et al., 2014; Rijkaart et al., 2012b).

Cross-sectional studies with short-term (2–3 year) CIN3+ risks:
-Required to evaluate the acceptability of triage strategies.

-Accepted short-term CIN3+ risk thresholds in the Netherlands:
- < 2%: maintain regular screening intervals
-2–20%: follow-up within 6–18 months required
- > 20%: direct referral for colposcopy

Follow-up studies with long-term (> 3 years) CIN3+ risks:
-Required to evaluate the extension of screening intervals.

4.2. Currently accepted triage strategies

4.2.1. Cytology with repeat cytology

Rijkaart et al. evaluated short-term CIN3+ risks within the Dutch VUSA-Screen cohort study (25,871 women screened with cytology and HPV co-testing) (Rijkaart et al., 2012a; Rijkaart et al., 2012c; Rijkaart et al., 2010). Results showed that HPV-positive women had a short-term CIN3+ risk of 13%. Highest short-term CIN3+ risks among HPV-positive women were observed for women with abnormal cytology (≥BMD): 42%. Consequently, HPV-positive women with abnormal cytology should be directly referred for colposcopy. Short-term CIN3+ risk of HPV-positive women with normal cytology was 5.2% and was between the 2% and 20% risk thresholds, indicating that follow-up testing of HPV-positive women with normal cytology is required. The short-term CIN3+ risk decreased to 1.6% when repeat cytology at 6 to 12 months follow-up was also normal, sufficiently low to maintain regular screening intervals. HPV-positive women with abnormal cytology at one year follow-up had a short-term CIN3+ risk of 25% and for these women, similar as for HPV-positive women with abnormal cytology at baseline, direct referral for colposcopy is required.

Additional evidence supporting triage of HPV-positive women with baseline and repeat cytology came from post-hoc analyses within the two Dutch cohorts of women screened with HPV and cytology co-testing (VUSA-Screen and POBASCAM), consisting of 1303 and 1100 HPV-positive women respectively (Dijkstra et al., 2014; Rijkaart et al., 2012b). In these post-hoc analyses, different triage strategies consisting of combinations of cytology, HPV testing and/or HPV-genotyping were evaluated. Triage strategies with baseline and repeat cytology performed well relative to other triage strategies with respect to NPV and PPV (resp. ~99% and ~36%)(Fig. 1) and colposcopy referral rates (~39%).

It should be noted that the performance of cytology and repeat cytology as a triage strategy largely depends on the quality of cytology, that varies widely among countries and is rather high in the Netherlands (Kitchener et al., 2006; Cuzick et al., 2006). Moreover, in the VUSA-Screen and POBASCAM studies cytology was read without knowledge of the HPV test result. In the new HPV-based screening programme, the HPV result is available, which is likely to lead to an increase in sensitivity at the cost of a decrease in specificity (Bergeron et al., 2015a; Moriarty et al., 2014; Richardson et al., 2015). This emphasizes the need for a more objective test for triage of HPV-positive women.

4.2.2. Cytology with HPV16/18-genotyping

A combination of cytology and HPV16/18-genotyping may achieve a clinical sensitivity that is high enough to obviate the need for repeat testing. This is an advantage as compliance with repeat testing is imperfect in real-life programmes. Multiple international studies evaluated the performance of combined cytology and HPV16/18-genotyping for triage of HPV-positive women. Despite the fact that several of these studies were not performed in population-based cohorts, overall results showed a high sensitivity for detection of CIN3+ and a limited PPV, resulting in high colposcopy referral rates (Castle et al., 2011; Wright Jr. et al., 2011). In the previously described post-hoc analyses within the VUSA-Screen and POBASCAM cohorts, NPV's for endpoint CIN3+ were 97.1% and 98.8%, respectively (Fig. 1) (Dijkstra et al., 2014; Rijkaart et al., 2012b). With the addition of repeat cytology, NPV estimates increased to 99.7% and 99.6%, respectively. However, the advantage of a baseline only triage strategy would then no longer apply.

Multiple studies have confirmed the clinical value of HPV16/18-genotyping. For that reason, HPV16/18-genotyping has been implemented in several guidelines in the USA (Massad et al., 2013). Compared to cytology with repeat cytology, HPV16/18-genotyping has a relatively low PPV for detection of CIN3+, both for the strategy consisting of cytology and HPV16/18-genotyping without repeat cytology (~27%) as for the strategy with repeat cytology (~26%). Because of this relatively high PPV, and because of the high quality of cytology in the Netherlands, cytology with repeat cytology is used for triage of HPV-positive women in the new Dutch screening programme. This choice has resulted in a relatively low colposcopy referral rate. However, a post-hoc analysis of the POBASCAM cohort evaluating several triage strategies using results from two consecutive HPV-based screening rounds, demonstrated that cytology with HPV16/18-genotyping would be a suitable strategy for triage of HPV-positive women in the second HPV-based screening round.

4.2.3. Repeat HPV testing

Testing for HPV clearance provides the highest protection against CIN3+ as women who have cleared the HPV infection are expected to have a very low CIN3+ risk. Several international studies showed that repeat HPV testing for triage of HPV-positive women has a high sensitivity for detection of CIN3+ (Naucler et al., 2009; Ronco et al., 2016). In the aforementioned post-hoc analyses, strategies that included repeat HPV testing showed very high NPV estimates. For example, the strategy consisting of baseline cytology with repeat HPV testing showed NPV estimates well above the 98% threshold (~100%). However, PPV estimates varied around 20% (~21%), resulting in relatively high colposcopy referral rates (~69%)(Fig. 1) (Dijkstra et al., 2014; Rijkaart et al., 2012b).

A recent post-hoc analysis performed within the POBASCAM cohort showed that HPV-positive women with a negative repeat HPV test after six to 18 months remain at increased HPV infection and high-grade CIN risk as compared to baseline HPV-negative women (Polman et al., 2017). It is hypothesized that a negative repeat HPV test does not always reflect actual HPV clearance, but can also be the result of a temporary decrease in viral load below the detection threshold of the HPV assay (Gravitt and Winer, 2017). These results indicate that screen HPV-positive women with a negative repeat HPV test and screen HPV-negative women require different long-term surveillance.

To conclude, strategies consisting of cytology with repeat cytology and/or HPV16/18 genotyping, and strategies including repeat HPV testing, seem acceptable for triage of HPV-positive women, as they have NPV estimates above 98% and PPV estimates above 20%. Within the Netherlands, it was decided to triage HPV-positive women with baseline cytology and repeat cytology after 6 months (Table 2). Cytology is repeated after 6 months to increase the sensitivity of the triage strategy (Dijkstra et al., 2014; Rijkaart et al., 2012b). The follow-up moment was set at 6 months in order to limit the risk of losing women to follow-up. In addition to the high NPV and PPV estimates that are achieved with this strategy, colposcopy referral rates are relatively low compared to other triage strategies. However, as the performance of the triage strategies and the accepted balance between safety and screening-related burden varies considerably between countries, different triage strategies might be more suitable in other countries. Moreover, additional research should be performed to evaluate the clinical performance of the currently established triage strategies in the second HPV-based screening round.

5. Adjustment of screening ages and intervals

European guidelines recommend primary HPV testing for women aged 35 years and older (von Karsa et al., 2015). Primary HPV testing in women under the age of 30 is not recommended as this is expected to lead to a considerable amount of overdiagnosis and overtreatment of potentially regressive CIN lesions, due to the high prevalence of transient HPV infections in women under 30. Guidelines do not recommend for or against primary HPV testing in women aged 30 to 34, due to a lack of evidence regarding this age category. In the Netherlands, cytology-based screening started at the age of 30. Results from the POBASCAM study showed that the cumulative detection of CIN3+ and CIN2+ over two consecutive HPV-based screening rounds did not differ between women aged 30–34 years and women aged 34 years and older in both study arms (HPV only versus HPV and cytology co-testing), indicating that there was no overdiagnosis in women aged 30–34 compared to women > 34 years. Consequently, the starting age of 30 was maintained in the new HPV-based screening programme in the Netherlands.

There is no evidence on the most optimal age to stop primary HPV-based screening. European guidelines recommend the same upper age limit as maintained for cytology-based screening (i.e. at age 60 to 65) (von Karsa et al., 2015). In the previous cytology-based screening programme, last screen was at 60 and this is maintained in the new screening programme. However, a negative HPV test is used as an exit test, meaning that women who test HPV-positive at age 60 are invited for an additional screen at age 65 to minimize the risk of cancer when exiting screening (Table 2). With this addition, the CIN3+ risk for women over 60 years of age is expected to be lower as compared to the previous cytology-based screening programme. Additional research should be performed to develop a potentially more appropriate follow-up and exit scheme for older women.

Long-term follow-up studies of women screened with HPV and cytology showed that HPV-negative women have very low long-term cervical cancer, CIN3+ and CIN2+ risks (Table 3A) (Uijterwaal et al., 2015; Dijkstra et al., 2016; Kitchener et al., 2011; Elfstrom et al., 2014; Castle et al., 2012). In the POBASCAM cohort, long-term CIN3+ risks in HPV-negative women aged 40 years and older were 72% lower than in HPV-negative women under 40. These results support an extension of the interval for HPV-negative women aged 40 years and older from five to 10 years. This extension has been included in the new HPV-based screening programme in the Netherlands. For HPV-negative women aged 30 or 35, screening intervals of five years are maintained (Table 2).

Long-term CIN3+ risks of HPV-positive women with a negative triage test have been analysed separately (Table 3B). Results show that HPV-positive women with a negative triage test (i.e. cytology combined with HPV16/18-genotyping and/or repeat cytology) remain to have non-negligible long-term CIN3+ risks: ~4% CIN3+ risk after five years follow-up and ~7% CIN3+ risk after 14 years follow-up (Uijterwaal et al., 2015; Dijkstra et al., 2016). Therefore, extension of the screening interval beyond five years cannot be justified, and a five year screening interval is maintained for these women.

Table 3
Long-term cancer, CIN3+ and CIN2+ risks in HPV-negative women (A) and HPV-positive women with negative triage (B).

Cohort	Follow-up period	Cancer risk	CIN3+ risk	CIN2+ risk
A. HPV-negative women				
VUSA-Screen[a]	5 years	–	0.09%	0.21%
POBASCAM[b]	14 years	0.09%	0.56%	–
ARTISTIC[c]	6 years	–	0.28%	0.87%
Swedescreen[d]	13 years	–	0.84%	1.74%
Kaiser Permanente[e]	18 years	–	0.90%	1.85%
B. HPV-positive, triage negative women				
Triage with cytology and repeat cytology				
VUSA-Screen[a]	5 years	–	4.1%	7.0%
POBASCAM[b]	14 years	–	~10.4%	–
Triage with cytology and HPV16/18-genotyping				
VUSA-Screen[a]	5 years	–	3.5%	7.9%
POBASCAM[b]	14 years	–	~8.7%	–

CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse.
[a] Uijterwaal et al. Cancer Prev Res, 2015.
[b] Dijkstra et al. BMJ, 2016.
[c] Kitchener et al. Eur J Cancer, 2011.
[d] Elfstrom et al. BMJ, 2014.
[e] Castle et al. J Clin Oncol, 2012.

6. Implementation of HPV self-sampling

In the Netherlands, approximately half of the cervical cancer cases occur in women not attending cervical screening (Bos et al., 2006). Studies have shown that offering HPV self-sampling to screening non-attendees increases participation rates (Virtanen et al., 2011; Giorgi Rossi et al., 2011; Szarewski et al., 2011; Gok et al., 2010; Gok et al., 2012; Verhoef et al., 2014a; Bosgraaf et al., 2015). In Dutch studies, self-sampling attendance rates up to 34% were observed among screening non-responders (Gok et al., 2010; Gok et al., 2012; Verhoef et al., 2014a; Bosgraaf et al., 2015; Bais et al., 2007). Based on these results, self-sampling is available on request in the new Dutch cervical screening programme. However, self-sampling is only recommended for women who do not want to visit their general practitioner (GP) for cervical sampling (Table 2) (Dutch Health Council, 2011).

Previous studies evaluating women their preferences indicated that a proportion of women who do normally attend clinician-based sampling for cervical screening would also prefer self-sampling (Sultana et al., 2015; Karjalainen et al., 2016; Virtanen et al., 2014; Bosgraaf et al., 2014). Moreover, implementation of self-sampling as a primary screening option could reduce the screening-related costs as it would greatly reduce the number of GP visits. However, before HPV self-sampling can be considered as a primary screening option, the clinical performance of HPV testing on self-collected samples as compared to clinician-collected samples needs to be assessed (Arbyn et al., 2014; Snijders et al., 2013). Previous studies comparing the clinical performance of HPV self-sampling and clinician-based sampling showed substantial variation, most likely due to the use of different self-sampling devices and HPV assays (Szarewski et al., 2007; Qiao et al., 2008; Belinson et al., 2012; Zhao et al., 2012; Guan et al., 2013; Nieves et al., 2013). A meta-analysis reviewing results of 36 self-sampling studies showed a similar sensitivity between HPV self-sampling and clinician-based HPV testing when a PCR-based HPV assay was used (Arbyn et al., 2014). Consequently, self-sampling in combination with a PCR-based HPV assay might be considered for routine screening.

The inclusion phase of a randomised paired screen-positive non-inferiority trial (i.e. the IMPROVE trial) comparing self-collected versus clinician-collected HPV testing in the Netherlands has recently been completed. Results show that HPV testing using a clinically validated PCR-based assay has similar accuracy for detection of CIN2+ and CIN3+ on self-collected and clinician-collected samples (Polman et al., 2018a). These results strongly support the use of HPV self-sampling as a primary screening method in routine screening. Moreover, a recent questionnaire study performed in the context of the IMPROVE trial shows that women from a regular screening population have a positive attitude towards self-sampling, and would prefer self-sampling in future screening (Polman et al., n.d.). It is expected that, based on these results, primary self-sampling will be introduced in the Netherlands in the near future.

Table 4
Overview of the expected changes in the screening-related costs and the adjustments that lead to these changes in costs.

	Yearly costs					Adjustments that lead to an increase/decrease in costs
	Cytology-based screening	HPV-based screening first five years[a] (%)		HPV-based screening after five years (%)		
Primary screening tests	€33.107.879	€26.554.658	(−20%)	€21.017.671	(−37%)	Decrease in costs due to: 1. Lower costs of the HPV assay as compared to cytology 2. Lower number of primary screening tests from five years after start of the new screening programme due to extension of screening intervals for HPV screen-negative women aged 40 and 50 years old 3. Lower costs of the primary screening test due to implementation of self-sampling for non-attendees, and possible future expansion of self-sampling as a primary screening instrument
Triage tests	€1.797.126	€2.472.471	(+38%)	€2.365.387	(+32%)	Increase in costs due to: 1. More triage tests due the higher sensitivity and lower specificity of the primary screening test 2. More repeat cytology due to the follow-up of HPV-positive women with normal baseline cytology
Colposcopy referrals and CIN treatments	€9.097.185	€18.631.951	(+105%)	€15.159.727	(+67%)	Increase in costs due to: 1. More colposcopy referrals and CIN treatments due to the higher sensitivity and lower specificity of the primary screening test
Cervical cancer treatments and palliative care	€1.826.234	€2.537.234	(+39%)	€1.767.761	(−3%)	Increase in costs due to: 1. Increased detection of cervical cancer in the first five years after start of the new screening programme due to the higher sensitivity of the primary screening test 2. Increased detection of cervical cancer in the first five years after start of the new screening programme due to implementation of HPV self-sampling for non-attendees
Total screening-related costs	€45.472.383	€50.196.314	(+10%)	€40.310.545	(−11%)	

Changes in costs are adapted from Naber et al., 2016.
[a] Average costs in the first five years after implementation of the new HPV-based screening programme; (%) difference as compared to cytology-based screening.

7. Colposcopy and histology

HPV-positive women with a positive triage test are referred to a gynaecologist for visual examination of the cervical transformation zone with a colposcope, allowing magnification for more accurate inspection. Application of acetic acid during colposcopy leads to the visible appearance of HPV-induced dysplasia. According to national guidelines, the colposcopist takes biopsies of all visible abnormalities (Oncoline: Guidelines Oncological Care, 2015). When no abnormalities are visible during colposcopy, it is advised to take two random biopsies in women with worse than BMD cytology, while biopsies can be omitted in women with BMD cytology.

Cervical histology specimens are graded according to the CIN classification (K, 2010; Arbyn et al., 2010; Bulten et al., 2011): in CIN1 dysplasia is seen in less than one third of the depth of the epithelium (mild dysplasia); in CIN2 dysplasia is seen in two thirds of the depth of the epithelium (moderate dysplasia); while in CIN3 dysplasia is seen in more than two thirds of the depth of the epithelium (severe dysplasia). When atypical cells invade the basal membrane, the lesion is graded as cervical cancer. All CIN lesions can progress, persist or regress. Treatment of CIN lesions is performed by a large loop excision of the transformation zone (LLETZ), in which the transformation zone and lesion are excised using a loop-shaped electric wire.

CIN3 has the lowest chance of spontaneous regression and is considered a true premalignant stage, and consequently, is always treated. In contrast, CIN1 is most often the result of a transient HPV infection and has the highest chance of spontaneous regression. Therefore, a wait-and-see policy with follow-up after one year is warranted. The chance of spontaneous regression of a CIN2 lesion is somewhere in between the regression chances of CIN1 and CIN3, however, remains very uncertain. Additionally, the diagnosis CIN2 has a low reproducibility (van Zummeren et al., 2018). Consequently, there is no uniform consensus regarding treatment of CIN2: women are often advised to undergo treatment in order to prevent possible progression to cancer, however, for women in their fertile life phase with a future child wish it can be decided, depending on the size of the lesion and the colposcopical aspect, to follow a wait-and-see policy (Oncoline: Guidelines Oncological Care, 2015). Because of the low reproducibility of CIN2, the WHO has introduced a two-tiered grading system in which lesions are subdivided in high-grade squamous intraepithelial lesions (HSIL; i.e. CIN2 and CIN3) and low-grade squamous intraepithelial neoplasia (LSIL; i.e. CIN1), which has been adopted in the USA (Massad et al., 2013; Darragh et al., 2012; *In WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Geneva*, 2013). However, as this system leads to a considerable amount of overtreatment of women with regressive HSIL, in most European countries, including the Netherlands, the CIN grading system is still used. Moreover, to minimize the amount of overtreatment when using the CIN grading system, an attempt is made to subdivide CIN2 in CIN1-like (wait-and-see policy) and CIN3-like lesions (need for immediate treatment) with additional immunohistochemical staining (e.g. p16 and/or Ki-67 staining) or biomarker testing (e.g. methylation marker analysis and/or HPV-E4) (von Karsa et al., 2015; van Zummeren et al., 2018; Steenbergen et al., 2014; van Baars et al., 2015). At this moment, both the CIN and the HSIL/LSIL grading systems are debatable. It is expected that, in the near future, a new classifying system based on biomarkers will be developed that better predicts the risk of cancer development and will therefore lead to more personalized treatment and less overtreatment.

8. Cost-effectiveness of the new Dutch screening programme

Several modelling studies showed that implementation of HPV-based cervical screening with cytology triage was likely to be cost-effective in the Netherlands (Berkhof et al., 2010; van Rosmalen et al., 2012; de Kok et al., 2012). Additional support comes from data of a modelling study that was conducted in preparation of the new cervical screening programme (Naber et al., 2016). Results showed that the new HPV-based screening programme is expected to be more effective in preventing cervical cancer and cervical cancer death than the previous cytology-based programme: 100 additional cervical cancer cases and 35 additional cervical cancer related deaths are expected to be prevented annually (Table 2) (Naber et al., 2016). The introduction of HPV self-sampling is expected to be a key factor for this higher effectiveness of the new programme as it increases screening participation rates.

The total screening-related costs consist of the following components: primary screening tests, triage tests, colposcopy referrals and CIN treatments, and cervical cancer treatments and palliative care. Table 4 provides an overview of the expected changes in the screening-related costs and the adjustments that lead to these changes in costs (Naber et al., 2016). The costs of the primary screening tests account for > 50% of the total costs and therefore greatly impact the total screening-related costs. In the first five years after implementation, the new HPV-based screening programme is expected to be more expensive than cytology-based screening as the increase in the costs of triage tests, colposcopy referrals and CIN treatments, and cervical cancer treatment and palliative care outnumber the decrease in the costs of the primary screening test, resulting in an increase of ~€5 million per year as compared to cytology-based screening. After five years the costs of the primary screening tests will decrease even further due to extension of the screening intervals for HPV-negative women aged 40 and 50, resulting in less screening moments. This decrease in costs outnumbers the increase of the other components, resulting in a total decrease of ~€5 million per year (~11%) as compared to cytology-based screening.

Collectively, the replacement of the cytology-based programme by the new HPV-based cervical screening programme in the Netherlands is expected to be effective and cost-saving (Naber et al., 2016). Whether implementation of HPV-based screening in other countries is cost-effective depends on decisions that will be made with regard to triage strategy, adjustment of screening ages and intervals, and implementation of self-sampling.

9. Conclusion

The Netherlands is one of the first countries worldwide to implement nationwide HPV-based screening and therefore may provide guidance to other countries. In this manuscript we discussed the rationale of the new Dutch cervical screening programme by reviewing the scientific evidence that contributed to the design of the new screening algorithm.

HPV-based screening was implemented in the Netherlands in 2017, as it has been shown to provide better protection against cervical precancer and cancer than cytology. Triage testing of HPV-positive women is required to identify HPV-positive women with underlying high-grade CIN. In the Netherlands, HPV-positive women are triaged with cytology and repeat cytology after 6 months. Screening intervals for HPV-negative women aged 40 years and older are extended from five to 10 years as HPV-negative women have very low long-term CIN3+ risks. For women under 40 and for HPV-positive women with negative triage, regular five-year screening intervals will be maintained. HPV self-sampling is implemented for screening non-responders, since this has been shown to be an effective strategy to attract non-attendees into screening.

The new screening algorithm is expected to annually prevent 100 additional cervical cancer cases and 35 additional cervical cancer related deaths as compared to the previous cytology-based screening programme. Implementation of the new HPV-based screening programme will result in an increase in costs during the first five years, but costs are expected to be lower as compared to cytology-based screening from five years after implementation of the new programme.

10. Future perspectives

Several other countries are expected to implement HPV-based screening in the coming years. The recent results of the IMPROVE trial, showing that HPV testing using a clinically validated PCR-based assay has similar accuracy for detection of CIN2+ and CIN3+ on self-collected and clinician-collected samples, are likely to enlarge role of self-sampling in cervical screening, making screening more accessible to women and increasing its efficiency.

Future research should focus on the development of more objective triage tests. Two promising techniques that have been investigated extensively are p16/Ki-67 dual-stained cytology (CINtec PLUS [Roche mtm laboratories AG, Mannheim, Germany]) and host cell DNA methylation marker analysis (QIAsure [Qiagen, Hilden, Germany] and PreCursor-M [Self-Screen B.V., Amsterdam, The Netherlands]). Several studies have shown the value of p16/Ki-67 dual-stained cytology for triage of HPV-positive women. However, the threshold for positivity of the assay is the presence of one single p16/Ki-67 positive cell, which demands the presence of sufficient intact cervical cells in a sample (Petry et al., 2011; Schmidt et al., 2011; Wentzensen et al., 2012; Ikenberg et al., 2013; Luttmer et al., 2016a; Bergeron et al., 2015b; Wentzensen et al., 2015; Ebisch et al., 2017; Wright Jr. et al., 2017). Consequently, p16/Ki-67 dual-stained cytology cannot be applied to self-samples. Although the research regarding methylation marker analysis for triage of HPV-positive women is ongoing, results up to now have proven that this technique is applicable on both self-collected and clinician-collected samples, opening the way to full molecular screening (Bierkens et al., 2013; De Strooper et al., 2014a; De Strooper et al., 2014b; Hesselink et al., 2014; Luttmer et al., 2016b; Overmeer et al., 2011; Verhoef et al., 2014b). Finally, monitoring of screening programmes remains of great importance, and linkage of HPV vaccination and screening registries will provide relevant information for further improvement of cervical screening. In the Netherlands, HPV vaccination has been introduced in 2009 for girls aged 12, with a catch-up programme for girls aged 13 to 16 (born in 1996 to 1993). These vaccinated girls will reach the screening starting age in 2023. However, also after 2023 screening will remain necessary as HPV vaccination uptake in the Netherlands is approximately 55% and is declining in the last years. The effectivity of the HPV vaccines is currently being evaluated. Depending on the results, especially those concerning cross-protection and herd immunity, adapted screening algorithms may be developed.

Conflict of interest

CJLMM is part-time director, and minority stock holder, of Self-Screen B.V., a spin-off company of VUmc, which owns patents on methylation markers and HPV detection, and has a very small number of Qiagen shares. Until April 2016 CJLMM had minority stock of Diassay B.V. CJLMMM has received speakers' fee from SPMSD/Merck, served occasionally on the scientific advisory board (expert meeting) of Qiagen, SPMSD/Merck and GSK. CJLMM has been co- investigator on a Sanofi Pasteur MSD sponsored trial, of which his institute received research funding.

PJFS has been on the speakers bureau of Roche diagnostics, Gen-Probe, Abbott, Qiagen and Seegene and has been a consultant for Crucell B.V, PJFS was minority shareholder of Self-Screen B.V.

JB has received consultancy fees from GlaxoSmithKline, and Merck/SPMSD and received travel support from DDL. All fees were collected by his employer.

NJP and GGK have no conflicts of interest to declare.

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References

Arbyn, M., Raifu, A.O., Weiderpass, E., et al., 2009. Trends of cervical cancer mortality in the member states of the European Union. Eur. J. Cancer 45, 2640–2648.
Arbyn, M., Anttila, A., Jordan, J., et al., 2010. European guidelines for quality Assurance in Cervical Cancer Screening. Second edition–summary document. Ann. Oncol. 21, 448–458.
Arbyn, M., Verdoodt, F., Snijders, P.J., et al., 2014. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol. 15, 172–183.
Arbyn, M., Snijders, P.J., Meijer, C.J., et al., 2015. Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening? Clin. Microbiol. Infect. 21, 817–826.
Bais, A.G., van Kemenade, F.J., Berkhof, J., et al., 2007. Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect non-responders in cervical screening programs. Int. J. Cancer 120, 1505–1510.
Baldur-Felskov, B., Munk, C., Nielsen, T.S., et al., 2015. Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997–2012. Cancer Causes Control 26, 1105–1116.
Belinson, J.L., Du, H., Yang, B., et al., 2012. Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing. Int. J. Cancer 130, 1855–1860.
Bergeron, C., Giorgi-Rossi, P., Cas, F., et al., 2015a. Informed cytology for triaging HPV-positive women: substudy nested in the NTCC randomized controlled trial. J. Natl. Cancer Inst. 107.
Bergeron, C., Ikenberg, H., Sideri, M., et al., 2015b. Prospective evaluation of p16/Ki-67 dual-stained cytology for managing women with abnormal Papanicolaou cytology: PALMS study results. Cancer Cytopathol. 123, 373–381.
Berkhof, J., Coupe, V.M., Bogaards, J.A., et al., 2010. The health and economic effects of HPV DNA screening in the Netherlands. Int. J. Cancer 127, 2147–2158.
Bierkens, M., Hesselink, A.T., Meijer, C.J., et al., 2013. CADM1 and MAL promoter methylation levels in hrHPV-positive cervical scrapes increase proportional to degree and duration of underlying cervical disease. Int. J. Cancer 133, 1293–1299.
Bos, A.B., Rebolj, M., Habbema, J.D., van Ballegooijen, M., 2006. Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. Int. J. Cancer 119, 2372–2375.
Bosgraaf, R.P., Ketelaars, P.J., Verhoef, V.M., et al., 2014. Reasons for non-attendance to cervical screening and preferences for HPV self-sampling in Dutch women. Prev. Med. 64, 108–113.
Bosgraaf, R.P., Verhoef, V.M., Massuger, L.F., et al., 2015. Comparative performance of novel self-sampling methods in detecting high-risk human papillomavirus in 30,130 women not attending cervical screening. Int. J. Cancer 136, 646–655.
Bulkmans, N.W., Berkhof, J., Rozendaal, L., et al., 2007a. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet 370, 1764–1772.
Bulkmans, N.W., Berkhof, J., Bulk, S., et al., 2007b. High-risk HPV type-specific clearance rates in cervical screening. Br. J. Cancer 96, 1419–1424.
Bulten, J., Horvat, R., Jordan, J., et al., 2011. European guidelines for quality assurance in cervical histopathology. Acta Oncol. 50, 611–620.
Castle, P.E., S, M., Jeronimo, J., Solomon, D., Schiffman, M., 2008. Risk Assessment to Guide the Prevention of Cervical Cancer. 12. pp. 1–7.
Castle, P.E., Stoler, M.H., Wright Jr., T.C., et al., 2011. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. Lancet Oncol. 12, 880–890.
Castle, P.E., Glass, A.G., Rush, B.B., et al., 2012. Clinical human papillomavirus detection forecasts cervical cancer risk in women over 18 years of follow-up. J. Clin. Oncol. 30, 3044–3050.
Castle, P.E., Smith, K.M., Davis, T.E., et al., 2015. Reliability of the Xpert HPV assay to detect high-risk human papillomavirus DNA in a colposcopy referral population. Am. J. Clin. Pathol. 143, 126–133.
Cervantes-Amat, M., Lopez-Abente, G., Aragones, N., et al., 2015. The end of the decline in cervical cancer mortality in Spain: trends across the period 1981-2012. BMC Cancer 15, 287.
Cuzick, J., Clavel, C., Petry, K.U., et al., 2006. Overview of the European and north American studies on HPV testing in primary cervical cancer screening. Int. J. Cancer 119, 1095–1101.
Darragh, T.M., Colgan, T.J., Cox, J.T., et al., 2012. The lower Anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. J. Low. Genit. Tract Dis. 16, 205–242.
de Kok, I.M., van der Aa, M.A., van Ballegooijen, M., et al., 2011. Trends in cervical cancer in the Netherlands until 2007: has the bottom been reached? Int. J. Cancer 128, 2174–2181.
de Kok, I.M., van Rosmalen, J., Dillner, J., et al., 2012. Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European

settings: cost effectiveness analysis based on a Dutch microsimulation model. BMJ 344, e670.
De Strooper, L.M., Hesselink, A.T., Berkhof, J., et al., 2014a. Combined CADM1/MAL methylation and cytology testing for colposcopy triage of high-risk HPV-positive women. Cancer Epidemiol. Biomark. Prev. 23, 1933–1937.
De Strooper, L.M., Meijer, C.J., Berkhof, J., et al., 2014b. Methylation analysis of the FAM19A4 gene in cervical scrapes is highly efficient in detecting cervical carcinomas and advanced CIN2/3 lesions. Cancer Prev. Res. (Phila.) 7, 1251–1257.
Dijkstra, M.G., van Niekerk, D., Rijkaart, D.C., et al., 2014. Primary hrHPV DNA testing in cervical cancer screening: how to manage screen-positive women? A POBASCAM trial substudy. Cancer Epidemiol. Biomark. Prev. 23, 55–63.
Dijkstra, M.G., van Zummeren, M., Rozendaal, L., et al., 2016. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. BMJ i4924, 355.
Dutch Health Council, 2011. Cervical Screening (In Dutch).
Ebisch, R.M., van der Horst, J., Hermsen, M., et al., 2017. Evaluation of p16/Ki-67 dual-stained cytology as triage test for high-risk human papillomavirus-positive women. Mod. Pathol. 30, 1021–1031.
Elfstrom, K.M., Smelov, V., Johansson, A.L., et al., 2014. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial. BMJ 348, g130.
Giorgi Rossi, P., Marsili, L.M., Camilloni, L., et al., 2011. The effect of self-sampled HPV testing on participation to cervical cancer screening in Italy: a randomised controlled trial (ISRCTN96071600). Br. J. Cancer 104, 248–254.
Gok, M., Heideman, D.A., van Kemenade, F.J., et al., 2010. HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. BMJ 340, c1040.
Gok, M., van Kemenade, F.J., Heideman, D.A., et al., 2012. Experience with high-risk human papillomavirus testing on vaginal brush-based self-samples of non-attendees of the cervical screening program. Int. J. Cancer 130, 1128–1135.
Gravitt, P.E., Winer, R.L., 2017. Natural history of HPV infection across the lifespan: role of viral latency. Viruses 9.
Guan, Y., Gravitt, P.E., Howard, R., et al., 2013. Agreement for HPV genotyping detection between self-collected specimens on a FTA cartridge and clinician-collected specimens. J. Virol. Methods 189, 167–171.
Hanselaar, A.G., 1995. The population-based screening for cervical cancer. A uniform framework for cytopathological diagnosis (In Dutch). Medisch Contact 50, 1590–1592.
Hesselink, A.T., Heideman, D.A., Steenbergen, R.D., et al., 2014. Methylation marker analysis of self-sampled cervico-vaginal lavage specimens to triage high-risk HPV-positive women for colposcopy. Int. J. Cancer 135, 880–886.
Ikenberg, H., Bergeron, C., Schmidt, D., et al., 2013. Screening for cervical cancer precursors with p16/Ki-67 dual-stained cytology: results of the PALMS study. J. Natl. Cancer Inst. 105, 1550–1557.
In WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Geneva.
Jordan, J., Arbyn, M., Martin-Hirsch, P., et al., 2008. European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1. Cytopathology 19, 342–354.
K, R.J., 2010. Blaustein's Pathology of the Female Genital Tract. Springer.
Karjalainen, L., Anttila, A., Nieminen, P., et al., 2016. Self-sampling in cervical cancer screening: comparison of a brush-based and a lavage-based cervicovaginal self-sampling device. BMC Cancer 16, 221.
Kitchener, H.C., Castle, P.E., Cox, J.T., 2006. Chapter 7: achievements and limitations of cervical cytology screening. Vaccine 24 (Suppl. 3), S3/63–70.
Kitchener, H.C., Almonte, M., Thomson, C., et al., 2009. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol. 10, 672–682.
Kitchener, H.C., Gilham, C., Sargent, A., et al., 2011. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. Eur. J. Cancer 47, 864–871.
Landy, R., Pesola, F., Castanon, A., Sasieni, P., 2016. Impact of cervical screening on cervical cancer mortality: estimation using stage-specific results from a nested case-control study. Br. J. Cancer 115, 1140–1146.
Luttmer, R., Dijkstra, M.G., Snijders, P.J., et al., 2016a. p16/Ki-67 dual-stained cytology for detecting cervical (pre)cancer in a HPV-positive gynecologic outpatient population. Mod. Pathol. 29, 870–878.
Luttmer, R., De Strooper, L.M., Berkhof, J., et al., 2016b. Comparing the performance of FAM19A4 methylation analysis, cytology and HPV16/18 genotyping for the detection of cervical (pre)cancer in high-risk HPV-positive women of a gynecologic outpatient population (COMETH study). Int. J. Cancer 138, 992–1002.
Massad, L.S., Einstein, M.H., Huh, W.K., et al., 2013. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J. Low. Genit. Tract Dis. 17, S1–S27.
Mayrand, M.H., Duarte-Franco, E., Rodrigues, I., et al., 2007. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N. Engl. J. Med. 357, 1579–1588.
Meijer, C.J., Berkhof, J., 2012. Screening: Cervical cancer–should we abandon cytology for screening? Nat. Rev. Clin. Oncol. 9, 558–559.
Meijer, C.J., Berkhof, J., Castle, P.E., et al., 2009. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int. J. Cancer 124, 516–520.
Moriarty, A.T., Nayar, R., Arnold, T., et al., 2014. The Tahoe study: bias in the interpretation of Papanicolaou test results when human papillomavirus status is known. Arch. Pathol. Lab. Med. 138, 1182–1185.
Munoz, N., Castellsague, X., de Gonzalez, A.B., Gissmann, L., 2006. Chapter 1: HPV in the etiology of human cancer. Vaccine 24 (Suppl. 3), S3/1–10.
Naber, S.K., Matthijsse, S.M., Jansen, E.E.L., d K, I., M., M.C., de Koning, H.J., van Ballegooijen, M., 2016. Effects of the New Cervical Screening Programme in the Netherlands Following Recent Developments (In Dutch).
Nanda, K., McCrory, D.C., Myers, E.R., et al., 2000. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann. Intern. Med. 132, 810–819.
Naucler, P., Ryd, W., Tornberg, S., et al., 2007. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N. Engl. J. Med. 357, 1589–1597.
Naucler, P., Ryd, W., Tornberg, S., et al., 2009. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J. Natl. Cancer Inst. 101, 88–99.
Nieves, L., Enerson, C.L., Belinson, S., et al., 2013. Primary cervical cancer screening and triage using an mRNA human papillomavirus assay and visual inspection. Int. J. Gynecol. Cancer 23, 513–518.
Oncoline: Guidelines Oncological Care, 2015. Guideline CIN, AIS and VAIN (in Dutch).
Overmeer, R.M., Louwers, J.A., Meijer, C.J., et al., 2011. Combined CADM1 and MAL promoter methylation analysis to detect (pre-)malignant cervical lesions in high-risk HPV-positive women. Int. J. Cancer 129, 2218–2225.
Papanicolaou, G.N., 1942. A new procedure for staining vaginal smears. Science 95, 438–439.
Peto, J., Gilham, C., Fletcher, O., Matthews, F.E., 2004. The cervical cancer epidemic that screening has prevented in the UK. Lancet 364, 249–256.
Petry, K.U., Schmidt, D., Scherbring, S., et al., 2011. Triaging pap cytology negative, HPV positive cervical cancer screening results with p16/Ki-67 dual-stained cytology. Gynecol. Oncol. 121, 505–509.
Poljak, M., Kocjan, B.J., Ostrbenk, A., Seme, K., 2016. Commercially available molecular tests for human papillomaviruses (HPV): 2015 update. J. Clin. Virol. 76 (Suppl. 1), S3–S13.
Polman, N.J., Veldhuijzen, N.J., Heideman, D.A.M., et al., 2017. HPV-positive women with normal cytology remain at increased risk of CIN3 after a negative repeat HPV test. Br. J. Cancer 117, 1557–1561.
Polman, N.J., Ebisch, R.M., Heideman, D.A., et al., 2018a. Clinical performance of HPV testing on self-collected versus clinician-collected samples: results of a randomised paired screen-positive non-inferiority trial. Lancet Oncol (In press).
Polman, N.J., de Haan, Y., Veldhuijzen, N.J., et al., 2018b. Experience with HPV self-sampling and clinician-based sampling in women attending routine cervical screening in the Netherlands. Prev. Med (Submitted for publication).
Qiao, Y.L., Sellors, J.W., Eder, P.S., et al., 2008. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. Lancet Oncol. 9, 929–936.
Richardson, L.A., El-Zein, M., Ramanakumar, A.V., et al., 2015. HPV DNA testing with cytology triage in cervical cancer screening: influence of revealing HPV infection status. Cancer Cytopathol. 123, 745–754.
Rijkaart, D.C., Coupe, V.M., van Kemenade, F.J., et al., 2010. Comparison of hybrid capture 2 testing at different thresholds with cytology as primary cervical screening test. Br. J. Cancer 103, 939–946.
Rijkaart, D.C., Berkhof, J., Rozendaal, L., et al., 2012a. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol. 13, 78–88.
Rijkaart, D.C., Berkhof, J., van Kemenade, F.J., et al., 2012b. Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. Int. J. Cancer 130, 602–610.
Rijkaart, D.C., Berkhof, J., van Kemenade, F.J., et al., 2012c. HPV DNA testing in population-based cervical screening (VUSA-screen study): results and implications. Br. J. Cancer 106, 975–981.
Ronco, G., Giorgi-Rossi, P., Carozzi, F., et al., 2010. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 11, 249–257.
Ronco, G., Zappa, M., Franceschi, S., et al., 2016. Impact of variations in triage cytology interpretation on human papillomavirus-based cervical screening and implications for screening algorithms. Eur. J. Cancer 68, 148–155.
Sasieni, P., Adams, J., Cuzick, J., 2003. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br. J. Cancer 89, 88–93.
Schiffman, M., Castle, P.E., Jeronimo, J., et al., 2007. Human papillomavirus and cervical cancer. Lancet 370, 890–907.
Schmidt, D., Bergeron, C., Denton, K.J., et al., 2011. p16/ki-67 dual-stain cytology in the triage of ASCUS and LSIL papanicolaou cytology: results from the European equivocal or mildly abnormal Papanicolaou cytology study. Cancer Cytopathol. 119, 158–166.
Sherman, M.E., Lorincz, A.T., Scott, D.R., et al., 2003. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J. Natl. Cancer Inst. 95, 46–52.
Smith, M.A., Edwards, S., Canfell, K., 2017. Impact of the National Cervical Screening Programme in New Zealand by age: analysis of cervical cancer trends 1985–2013 in all women and in Maori women. Cancer Causes Control 28, 1393–1404.
Snijders, P.J., Verhoef, V.M., Arbyn, M., et al., 2013. High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening. Int. J. Cancer 132, 2223–2236.
Solomon, D., Davey, D., Kurman, R., et al., 2002. The 2001 Bethesda system: terminology for reporting results of cervical cytology. JAMA 287, 2114–2119.
Steenbergen, R.D., Snijders, P.J., Heideman, D.A., Meijer, C.J., 2014. Clinical implications of (epi)genetic changes in HPV-induced cervical precancerous lesions. Nat. Rev. Cancer 14, 395–405.
Stoler, M.H., Schiffman, M., 2001. Atypical squamous cells of undetermined significance-

low-grade squamous intraepithelial lesion triage study G. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL triage study. JAMA 285, 1500–1505.
Sultana, F., Mullins, R., English, D.R., et al., 2015. Women's experience with home-based self-sampling for human papillomavirus testing. BMC Cancer 15, 849.
Szarewski, A., Cadman, L., Mallett, S., et al., 2007. Human papillomavirus testing by self-sampling: assessment of accuracy in an unsupervised clinical setting. J. Med. Screen. 14, 34–42.
Szarewski, A., Cadman, L., Mesher, D., et al., 2011. HPV self-sampling as an alternative strategy in non-attenders for cervical screening - a randomised controlled trial. Br. J. Cancer 104, 915–920.
Uijterwaal, M.H., Polman, N.J., Van Kemenade, F.J., et al., 2015. Five-year cervical (pre)Cancer risk of women screened by HPV and cytology testing. Cancer Prev. Res. (Phila.) 8, 502–508.
van Baars, R., Griffin, H., Wu, Z., et al., 2015. Investigating diagnostic problems of CIN1 and CIN2 associated with high-risk HPV by combining the novel molecular biomarker PanHPVE4 with P16INK4a. Am. J. Surg. Pathol. 39, 1518–1528.
van der Aa, M.A., Pukkala, E., Coebergh, J.W., et al., 2008. Mass screening programmes and trends in cervical cancer in Finland and the Netherlands. Int. J. Cancer 122, 1854–1858.
van Rosmalen, J., de Kok, I.M., van Ballegooijen, M., 2012. Cost-effectiveness of cervical cancer screening: cytology versus human papillomavirus DNA testing. BJOG 119, 699–709.
van Zummeren, M., Leeman, A., Kremer, W.W., et al., 2018. Three-tiered score for Ki-67 and p16(ink4a) improves accuracy and reproducibility of grading CIN lesions. J. Clin. Pathol. 71, 981–988.
Verhoef, V.M., Bosgraaf, R.P., van Kemenade, F.J., et al., 2014a. Triage by methylation-marker testing versus cytology in women who test HPV-positive on self-collected cervicovaginal specimens (PROHTECT-3): a randomised controlled non-inferiority trial. Lancet Oncol. 15, 315–322.
Verhoef, V.M., Heideman, D.A., van Kemenade, F.J., et al., 2014b. Methylation marker analysis and HPV16/18 genotyping in high-risk HPV positive self-sampled specimens to identify women with high grade CIN or cervical cancer. Gynecol. Oncol. 135, 58–63.
Vink, M.A., Bogaards, J.A., van Kemenade, F.J., et al., 2013. Clinical progression of high-grade cervical intraepithelial neoplasia: estimating the time to preclinical cervical cancer from doubly censored national registry data. Am. J. Epidemiol. 178, 1161–1169.
Virtanen, A., Anttila, A., Luostarinen, T., Nieminen, P., 2011. Self-sampling versus reminder letter: effects on cervical cancer screening attendance and coverage in Finland. Int. J. Cancer 128, 2681–2687.
Virtanen, A., Nieminen, P., Niironen, M., et al., 2014. Self-sampling experiences among non-attendees to cervical screening. Gynecol. Oncol. 135, 487–494.
von Karsa, L., A., M., De Vuyst, H., Dillner, J., Dillner, L., Franceschi, S., Patnick, J., Ronco, G., Segnan, N., Suonio, E., Törnberg, S., Antilla, A., 2015. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus Res. 1, 22–31.
Walboomers, J.M., Jacobs, M.V., Manos, M.M., et al., 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J. Pathol. 189, 12–19.
Wentzensen, N., Schwartz, L., Zuna, R.E., et al., 2012. Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. Clin. Cancer Res. 18, 4154–4162.
Wentzensen, N., Fetterman, B., Castle, P.E., et al., 2015. p16/Ki-67 dual stain cytology for detection of cervical precancer in HPV-positive women. J. Natl. Cancer Inst. 107, djv257.
Wentzensen, N., Arbyn, M., Berkhof, J., et al., 2017. Eurogin 2016 roadmap: how HPV knowledge is changing screening practice. Int. J. Cancer 140, 2192–2200.
Wright Jr., T.C., Stoler, M.H., Sharma, A., et al., 2011. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am. J. Clin. Pathol. 136, 578–586.
Wright Jr., T.C., Behrens, C.M., Ranger-Moore, J., et al., 2017. Triaging HPV-positive women with p16/Ki-67 dual-stained cytology: results from a sub-study nested into the ATHENA trial. Gynecol. Oncol. 144, 51–56.
Zhao, F.H., Lewkowitz, A.K., Chen, F., et al., 2012. Pooled analysis of a self-sampling HPV DNA test as a cervical cancer primary screening method. J. Natl. Cancer Inst. 104, 178–188.
zur Hausen, H., 2002. Papillomaviruses and cancer: from basic studies to clinical application. Nat. Rev. Cancer 2, 342–350.