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# A model to evaluate the costs and clinical effectiveness of human papilloma virus screening compared with annual papanicolaou cytology in Germany

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ABSTRACT

*Objectives:* We modelled human papilloma virus (HPV) primary screening scenarios compared with Pap cytology to evaluate clinical effectiveness and projected annual costs in Germany.
*Study design:* A Markov cohort model was built to compare the budget impact of annual Pap cytology with different 5-yearly HPV screening scenarios: (1) a positive HPV test followed by Pap cytology; (2) a positive HPV test followed by p16/Ki-67 dual-stained cytology; (3) a positive HPV test followed by colposcopy if HPV-16/18-positive or p16/Ki-67 dual-stained cytology if positive for other subtypes; (4) co-testing with HPV and Pap. Screening scenarios were based on a 10-year horizon.
*Results:* All HPV screening scenarios in the model were associated with fewer deaths from missed diagnosis of cervical cancer compared with Pap screening; 10-year totals n = 172–344 (1.5–3 per 100,000) versus n = 477 (4.1 per 100,000), respectively. Total annual costs were lower with HPV screening than Pap cytology. The projected average annual cost for HPV screening ranged from €117 million to €136 million compared with €177 million for Pap screening, representing annual savings of €41–60 million. The greatest clinical impact was achieved with primary HPV screening (with genotyping) followed by colposcopy for HPV 16/18-positive women or p16/Ki-67 dual-stained cytology for women positive for other HPV subtypes.
*Conclusion:* Screening strategies including primary HPV testing for high-risk subtypes (HPV-16/18) in conjunction with p16/Ki-67 dual-stained cytology can improve the detection of cervical cancer at a lower total annual cost than conventional Pap cytology screening.



## Introduction

Human papilloma virus (HPV) testing is being widely integrated into primary screening programs for cervical cancer in women older than 25–30 years, based on compelling evidence showing superior sensitivity, reliability and reproducibility compared with Pap cytology [1–3]. HPV-DNA is present in 95–100% of cervical cancers and almost all cases are attributable to high-risk HPV subtypes, predominately HPV-16 and −18 [4,5]. HPV testing with genotyping screens for all high-risk genotypes and identifies cases positive for HPV-16 or −18 who would benefit from immediate intervention [6]. In addition, Pap screening more frequently than every 5 years is not necessary in HPV-negative women [7]. The effectiveness of HPV screening may be improved by use with p16/Ki-67 dual-stained cytology, which combines superior sensitivity and non-inferior specificity over Pap cytology for detecting high-grade cervical intraepithelial neoplasia (CIN2+) [8].

Cervical cancer incidence (9.7 per 100,000 annually) and mortality (2.4 per 100,000 annually) rates remain relatively high in Germany [9,10]. Within the framework of the German national cancer plan, and based on a systematic review by the Institute for Quality and Efficiency in Healthcare (IQWiG), the General Federal Committee (Gemeinsamer Bundesausschuss; G-BA) decided in 2015 to implement primary HPV screening for women aged 35 years or older [11,12] (see Supplementary Table S1). In the first phase, approved in 2016, screening will consist of a primary HPV

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test combined with Pap smear co-testing every 3 years ('combination model'). To prevent over-diagnosis following primary HPV screening, the German S-3 guideline recommends three triage tests for women with a positive HPV test: (1) Pap cytology, (2) p16/Ki-67 dual-stained cytology, and (3) colposcopy for women positive for HPV-16 or −18 [11].

We modelled the clinical and budgetary impact for payer organizations of the three HPV-based cervical cancer screening scenarios recommended in the German S-3 guidelines and the 'combination model' recommended by the G-BA. Our objective was to compare these HPV primary screening scenarios with Pap cytology in terms of clinical effectiveness (cervical cancers avoided) and costs of screening, diagnosis, and subsequent treatment.

## Materials and methods

A Markov cohort model was built to estimate the budget impact of screening for HPV and subsequent diagnosis of CIN2+ disease, CIN, and cervical cancer (Supplementary Appendix A). Women enter the decision-tree with the probability of initial disease representative of a population aged 30–65 years screened for cervical cancer in Germany. This age range is aligned with the G-BA proposal. All scenarios consider a similar time horizon (10 years for a 5-year HPV interval or 6 years for a 3-year HPV interval). A 5-yearly interval was chosen based on the findings of previous studies [6], while the 3-yearly model was included to reflect the interval in the G-BA's interim 'combination model'.

### *Screening scenarios*

Annual Pap cytology provides the baseline reference for comparisons with four representative strategies based on primary HPV testing, with or without reflex Pap cytology and p16/Ki-67 dual-stained cytology. In the annual Pap cytology scenario (Fig. 1), reflex HPV testing is done immediately in 50% of the women with atypical squamous cells of undetermined significance (ASC-US) and in the other half a re-test with Pap cytology is done after 1 year. Of the women with low-grade squamous intraepithelial lesion (LSIL), 50% have a re-test with Pap cytology after 1 year, 20% have reflex HPV testing and 30% undergo colposcopy. Colposcopy is performed in all women with high-grade squamous intraepithelial lesion (HSIL). Women with negative results return to routine Pap cytology every year. Fig. 2 depicts the decision-tree diagrams for the four screening scenarios, which have a 5-year (or 3-year) interval for HPV testing compared with a 1-year interval for Pap cytology. The scenarios are described in detail in Table 1.

These scenarios assume women see their doctor at least once a year, with a screening attendance rate of 72% [13,14], compliance rates of 45% for Pap and 80% for HPV [15–19], and an adoption rate for p16/Ki-67 dual-stained cytology of 95% (see Supplementary Table S2).

### *Model inputs and assumptions*

The model is populated with data to assess the clinical and budgetary impact of different screening scenarios in Germany, assuming a total population of 80.5 million, with 16 million women aged 30–65 years eligible for screening after excluding ineligible individuals, such as hysterectomized women, and a screened population of 11.5 million (assuming 72% attendance). Epidemiological data for Germany were used [6,20,21], while test performance inputs were taken from the ATHENA (Addressing THE Need for Advanced HPV Diagnostics HPV: high-risk Human Papilloma Virus) trial [1,22,23] and are based on women ≥30 years. HPV test performance in ATHENA is comparable to studies conducted in Germany and provides representative data for the purpose of the model [6,21]. Model inputs were based on the entire cohort and not stratified by age. Data for the natural history of cervical cancer were taken from the literature (supplementary Table S2). In the model, CIN2 cases are not treated and it is assumed that high-risk HPV-infection, including HPV-16/18 and 12 other subtypes, can progress through CIN3 to invasive cervical cancer. The model considers both death through cervical cancer and all-cause mortality. Two surveillance arms were modelled. In the current standard arm, Pap cytology is done at 6-month intervals for 3 years and in the HPV primary screening arm, co-testing is done after 6 and 24 months. Women diagnosed with CIN2+ remain in

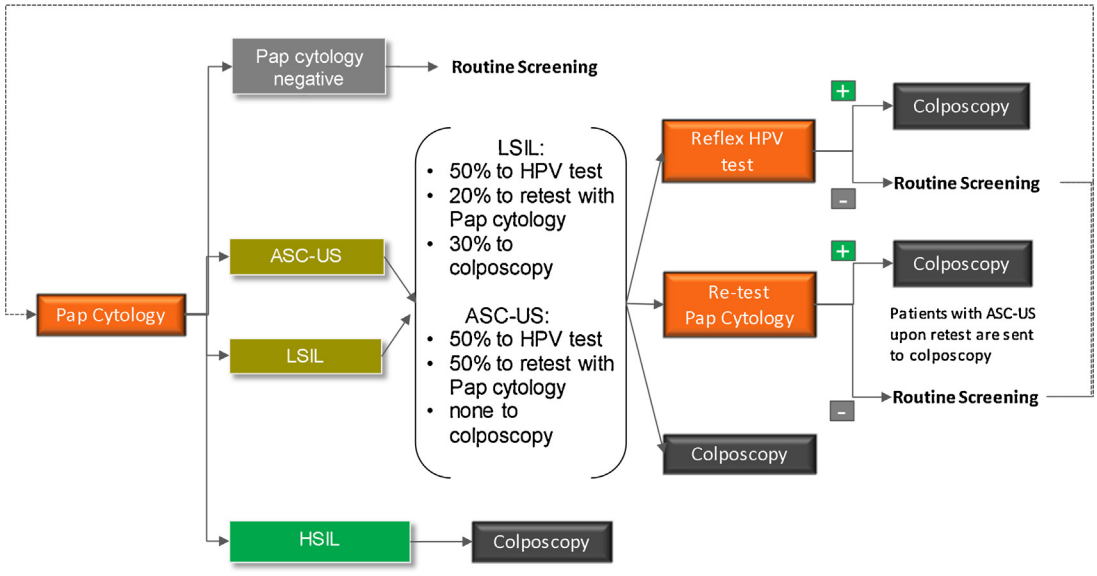


**Fig. 1.** Annual cytological cervical cancer screening, the standard screening approach in Germany prior to the introduction of primary HPV screening for women over 30 years. The figure shows assumptions used in the model for comparison with different HPV screening scenarios. The model considers only women aged over 30 years undergoing Pap screening. It is assumed that reflex HPV testing and colposcopy are done 'immediately', where indicated, and Pap cytology is retested after 1 year.