

An economic analysis of human papillomavirus triage for the management of women with atypical and abnormal Pap smear results in Germany

Sara K. Sheriff · K. Ulrich Petry · Hans Ikenberg ·
Geoffrey Crouse · Peter D. Mazonson ·
Christopher C. Santas

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Abstract We developed decision-analytic models to determine the cost effectiveness of incorporating human papillomavirus (HPV) testing into the management of atypical and abnormal Pap smear results in Germany. The models compare three management strategies: (1) repeat Pap smear, (2) triage with HPV DNA testing, or (3) immediate treatment. The primary outcome measure is incremental cost per case of cervical intraepithelial neoplasia (CIN) 2+ detected and treated. The models take the perspective of the German health system. For patients with initial PapIIw, III, and IIId results, incremental cost effectiveness ratios for HPV triage versus repeat Pap smears are €2,232, €815, and €487 per additional case of CIN2+ detected and treated. In addition, the number of cases of CIN2+ detected and treated in a hypothetical population of 1,000 women increases from 17 to 35, 61 to 130, and 157 to 332 for each population, respectively. For patients with initial PapIII and IIId results, immediate treatment of 1,000 patients detects only four and 11

additional cases of CIN2+ versus HPV triage at incremental cost effectiveness ratios of €39,684 and €10,716 per case, respectively. For each of the populations evaluated, HPV triage is the most cost-effective management strategy versus either repeat Pap smear or immediate treatment.

Keywords Human papillomavirus · Cervical cancer · Cost effectiveness · Pap smear · Germany

Introduction

Cervical cancer is the second most common cancer in women worldwide, with almost 500,000 new cases of invasive cervical cancer diagnosed and more than 270,000 women dying from the disease each year. In the European Union as a whole, there are over 32,000 new cases each year, and approximately 14,000 deaths, with over 6,000 of these cases and almost 3,000 of these deaths occurring in Germany. Germany's cervical cancer incidence and mortality rates (14.7 and 7.1 cases per 100,000) are among the highest in Europe [1].

Cervical cancer screening based on cervical cytology (the Papanicolaou smear) has been credited with substantial reductions in cervical cancer in those countries where it has been effectively implemented [2–6]. However, cervical cancer screening based on the Pap smear is limited in several key aspects, most notably with regard to the appropriate follow-up of women with atypical or mildly abnormal smear results [7]. In Germany, which grades Pap smears in accordance with the Second Munich Cytological Classification, such smears include PapIIw (inadequate specimens, minimal dysplastic changes, equivalent to atypical squamous cells of

S. K. Sheriff · P. D. Mazonson · C. C. Santas (✉)
Mosaic Health Care Consultants,
15 Hillcrest Avenue,
Larkspur, CA 94939, USA
e-mail: ccsantas@earthlink.net

K. U. Petry
Department of Obstetrics and Gynecology,
Klinikum der Stadt Wolfsburg, Wolfsburg, Germany

H. Ikenberg
Boersch-Ikenberg,
Laboratory for Cytology and Molecular Diagnostics,
Frankfurt, Germany

G. Crouse
Roche Diagnostics, Basel, Switzerland

undetermined significance—unofficial category), PapIII (important degenerative, inflammatory or iatrogenic changes of the cells where benignity or malignancy cannot be diagnosed with certainty even if the smear is adequately prepared), and PapIIIId [mild-to-moderate dysplasia, cervical intraepithelial neoplasia (CIN) I and II] [8]. In a recent prospective cohort study of 8,466 women undergoing routine cervical cancer screening in Hanover, Tübingen and surrounding areas, 3.0% of women had atypical or mildly abnormal Pap results [9].

While the majority of women in categories IIw, III, and IIIId will not require treatment, it has been established that between 6% and 10% will have underlying high-grade disease, cervical intraepithelial neoplasia grade 2 or higher (CIN2+), requiring immediate treatment [4, 10]. The problem is one of identifying this important sub-group [11]. Substantial variation exists among German practitioners regarding the management of women with initial Pap results of PapIIw, PapIII, and PapIIIId, and alternative guidelines describe a number of acceptable approaches [12, 13]. Management strategies range from immediate treatment with conization to repeating cytology tests as many as four times in 1 year before making a decision to treat. Another more recent approach involves testing for high-risk human papillomavirus (HPV) DNA. Research has shown that greater than 99% of all invasive cervical cancers contain high-risk HPV, and, as a result, the virus has been designated as a “necessary cause” of cervical cancer and a majority of its precursor lesions [14]. The introduction of HPV testing as an adjunct to routine cervical cancer screening brings with it the potential to improve screening effectiveness by detecting higher percentages of high-grade lesions and also to eliminate unnecessary diagnostic follow-up and treatment in women who are HPV negative.

In Germany, variation in patient management is driven, in part, by individual physician preferences, but treatment decisions also reflect the reimbursement environment and subsequent availability of potential diagnostic procedures. Histological evaluation, involving the use of expert colposcopy and biopsy, is considered to be the gold standard for detecting high-grade cervical lesions and carcinoma in women who present with atypical or abnormal Pap results [15]. In the UK, France, and the USA, histological evaluation is commonly used to identify women with atypical or abnormal results who are found to be HPV positive. Because the cost of expert colposcopy is not currently reimbursed in Germany and is unavailable in the majority of the country, it has not been included in this analysis [16]. Similarly, liquid-based cytology (LBC), which has demonstrated improved sensitivity but is more costly

than conventional cytology, is not widely available in Germany and has also been excluded from this study. Subsequent analyses will be necessary to address the cost effectiveness of HPV triage when such procedures become more widely available in Germany.

We designed three decision-analytic models to evaluate the cost effectiveness of various strategies used to manage women with screening results of PapIIw, PapIII, and PapIIIId. Potential strategies included: (1) repeat Pap test; (2) triage with HPV testing; and (3) immediate treatment (PapIII and IIIId only).

Models

Figure 1 presents simplified model diagrams for women with PapIIw or PapIII/PapIIIId at screening. The first branching point (designated by a small box) represents a decision node. This decision node corresponds to the initial choice of follow-up strategy for women entering into the model. Estimates of the prevalence of CIN2+ in the starting populations, as well as data regarding individual test sensitivities and specificities, are used to estimate: (1) the proportion of women for whom CIN2+ is detected and treated; (2) the proportion of women with CIN2+ that is not detected; (3) the proportion of women with <CIN2 that receives unnecessary treatment.

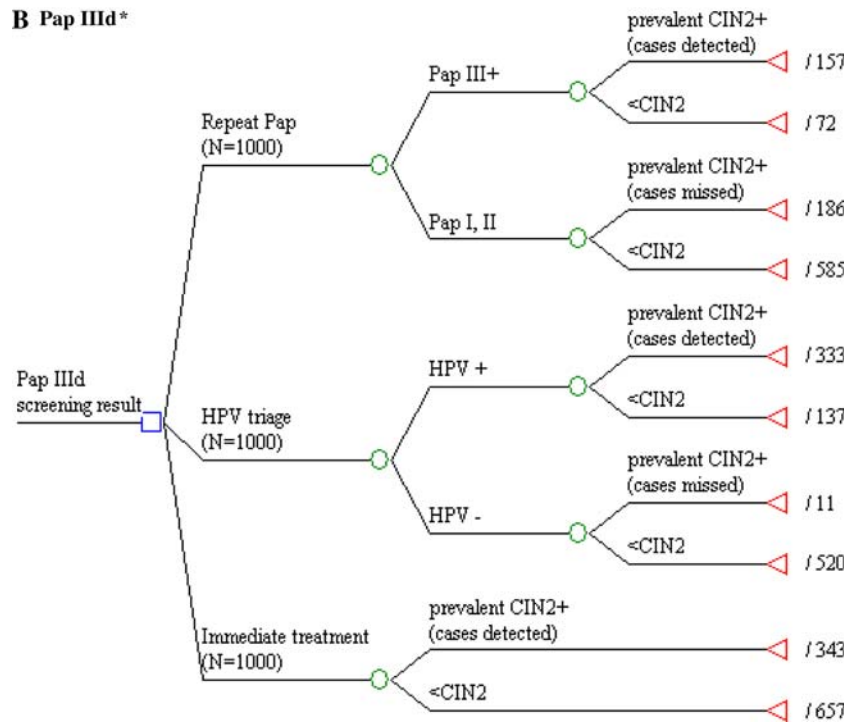
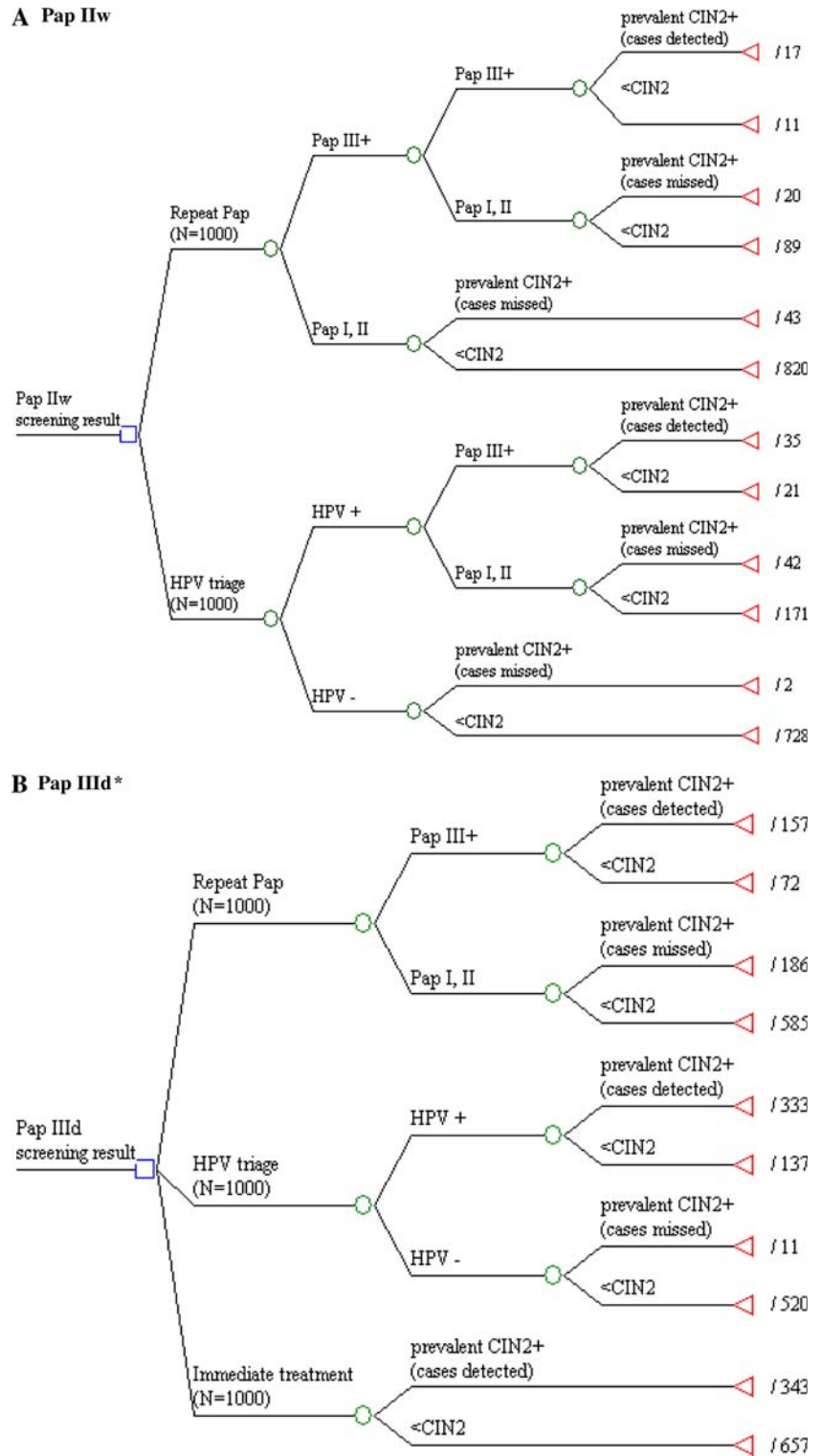
Each model simulates 1 year of follow-up for women with atypical or abnormal cervical cancer screening results. The primary outcome is incremental cost effectiveness, defined as the additional cost per case of CIN2+ detected and treated, relative to the next less costly alternative. The base-case models assume the perspective of the German health system and, as such, consider only the direct costs of medical care.

Women with atypical or abnormal Pap results at routine cervical cancer screening require additional follow-up. The treatment and management decisions in the model are based on a combination of current German guidelines, common clinical practice, and expert opinion. The model assumes the following treatment and management strategies for cytology results classified as PapIIw or PapIII/IIIId.

PapIIw

Women who enter into the model with an initial screening result of PapIIw are managed by one of the following strategies, (1) repeat Pap (treatment follows three consecutive positive Pap results); or (2) triage using results of HPV testing (repeat Pap if HPV positive).

Fig. 1 Decision-analytic model of follow-up for atypical and abnormal cervical cancer screening results. **a** Pap IIw, **b** Pap IIIId. *The decision-analytic model structure for PapIII is identical to that for Pap IIIId



Women who are managed by repeat Pap test are followed-up for retesting 3 months after their initial screen. If results of the repeat Pap are positive (i.e., PapIII+), women return for a second repeat Pap in

3 months. If results of the second repeat Pap are positive, women are referred for treatment with cold-knife conization or large loop excision of the transformation zone (LLETZ). Women with a first or

second repeat Pap result of PapI or PapII require no additional follow-up and return to routine screening the following year.

Women who are managed by HPV triage are followed-up with HPV sample collection and testing 3 months after their initial screening. If HPV test results are positive, women return for repeat Pap testing in 3 months. If repeat Pap is PapIII+, women are referred for treatment. If results are PapI or PapII, women are followed-up the following year.

PapIII/IIId

For the purposes of the model, management strategies for women with a screening result of PapIII or IIId do not differ. Potential strategies include the following: (1) repeat Pap (treat if repeat Pap results are positive); (2) triage using results of HPV testing (treat if HPV is positive); (3) immediate treatment.

In the case of PapIII and PapIIId, for women who are managed by repeat Pap test, the decision to treat is made after a single positive repeat Pap result. If results are PapIII or higher, women are referred for treatment. If results are PapI or II, women return to routine screening the following year. When HPV triage is used, women are referred to treatment if they are HPV positive. If HPV DNA results are negative, women return to routine screening.

Although the majority of women with a PapIII or IIId result at screening are followed-up at least once prior to undergoing treatment, immediate treatment does occur in some cases and has therefore been included as a management strategy in the model. In the case of immediate treatment, women are followed-up with Pap testing every 3 months for a maximum of 1 year, in accordance with current clinical guidelines.

To estimate the base-case probability inputs and costs for the various models, we abstracted data from the published literature, filling in the gaps as necessary with expert opinion (correspondence with K.U. Petry and H. Ikenberg). The values and sources for each of the model parameters are summarized in Tables 1 and 2. Unit costs for the resources identified in Table 2 were obtained using national Einheitlicher Bewertungsmaßstab (EBM) codes (this is the uniform valuation standard for the German fee schedule) and reimbursement levels. All costs are reported in euros at 2005 values.

Various assumptions were made in the design of the models, including (1) compliance with screening, treatment, and follow-up is 100%; (2) initial screening is done using conventional cytology. In contrast to liquid-based cytology, conventional cytology requires

Table 1 Prevalence of CIN2+ and sensitivity/specificity for the detection of histologically confirmed CIN2+

Parameter	Base-case value	Sources
Prevalence of CIN2+		
PapIIw	0.080	Petry et al. [9]
PapIII	0.134	Schneider et al., unpublished data
PapIIId	0.343	Lonky et al. [17] Solomon et al. [18]
Sensitivity for CIN2+		
Repeat Pap	0.457	Arbyn et al. [19]
HPV DNA triage	0.969	Arbyn et al. [19] Solomon et al. [18] Petry et al. [9]
Specificity for CIN2+		
Repeat Pap	0.891	Arbyn et al. [19]
HPV DNA triage	0.791	Arbyn et al. [19] Petry et al. [9]

women who are managed with HPV triage to return for a second visit for sample collection; (3) sensitivity and specificity rates for repeat Pap and HPV testing are considered to be independent of baseline screening results (i.e., rates do not differ for women with PapIIw, PapIII, or PapIIId at initial screening); (4) sensitivity and specificity rates for a second repeat Pap are assumed to be equivalent to rates reported in the literature for first-time repeat Paps; (5) women with an initial result of PapIII or PapIIId who have a repeat Pap result of PapI, II, or IIw return for a follow-up visit in 3 months to have their negative repeat Pap result confirmed. The model assumes that such follow-up Pap test results are normal and that women will return to routine screening the following year.

Results

Table 3 presents the cost effectiveness and incremental cost effectiveness results for all strategies. For women who have an initial screening result of PapIIw, the incremental cost effectiveness of HPV triage versus repeat Pap smear is €2,232 per additional case of CIN2+ detected and treated. This value is slightly less than the average cost effectiveness of the repeat Pap strategy itself, which is €2,369. Consequently, while triage with HPV testing more than doubles the detection rate of CIN2+ relative to repeat Pap, it does so at a net decrease in the cost per case detected.

For women with a PapIII result, HPV triage again more than doubles the detection rate of CIN2+ relative to repeat Pap smear and is associated with an incremental cost effectiveness of €815 per case of CIN2+ detected. Compared to the average cost effectiveness

Table 2 Cost estimates

Parameter	Cost (2005 euros)	EBM code
Conventional cytology	11.03	01733; 40100
HPV DNA testing	40.00	Assumed
Office visit for follow-up Pap or HPV test	16.00	08211/08212; 08215
Large loop excision of the transformation zone (LLETZ)/knife-conization (outpatient procedure) ^a	304.46	08211/08212; 08215; 31301; 31502; 31695; 31821

^a Cost includes payment to physician but does not include cost for use of outpatient facility

Table 3 Cost effectiveness (C/E) of managing 1,000 women with initial Pap results of IIw, III and IIId

Strategy	Cost	Incremental cost	Effectiveness, number (%) ^a	Incremental effectiveness, number (%) ^b	Average C/E	Incremental C/E
IIw						
Repeat Pap	€40		17 (21)		€2,369	
HPV triage	€81	€41	35 (44)	19 (23)	€2,297	€2,232
III						
Repeat Pap	€100		61(46)		€1,629	
HPV triage	€156	€56	130 (97)	69 (51)	€1,198	€815
Immediate treatment	€321	€165	134 (100)	4 (3)	€2,391	€39,684
IIIId						
Repeat Pap	€121		157 (46)		€772	
HPV triage	€207	€86	332 (97)	176 (51)	€621	€487
Immediate treatment	€321	€114	343 (100)	11 (3)	€934	€10,716

^a Effectiveness is measured as the number of cases of CIN2+ detected and treated in the screening population [percentages are calculated as the number of detected cases of CIN2+ divided by the underlying prevalence of CIN2+ in each population (i.e., 8.0%, 13.4%, and 34.3%, for IIw, III, and IIIId, respectively)]

^b Incremental effectiveness and incremental C/E for the HPV triage arm are calculated relative to repeat Pap. Incremental effectiveness and incremental C/E for the immediate treatment arm are calculated relative to HPV triage (percentages are calculated as the arithmetic difference in overall effectiveness)

of managing women with repeat Pap, the incremental cost effectiveness of HPV triage is approximately 50% less (€815 vs €1,629). Immediate treatment detects an additional four cases of CIN2+ per 1,000 women, relative to HPV triage, at an incremental cost effectiveness of €39,684.

For women with an initial screening result of Pap-IIIId, repeat Pap is the least costly and also the least effective management strategy. At an incremental cost effectiveness of €487, managing women with HPV triage more than doubles the number of cases of CIN2+ detected (from approximately 16 cases per 100 women to 33 cases per 100). Compared to the average cost effectiveness of managing women with repeat Pap, the incremental cost effectiveness of HPV triage is approximately 37% less (€487 vs €772). Referring women with PapIIIId immediately for treatment detects all prevalent cases of CIN2+; however, it does so at an incremental cost effectiveness of €10,716 relative to HPV triage.

One-way sensitivity analyses were conducted on key model inputs to evaluate the degree to which results

were affected by changes to the base-case estimates. Cost inputs were varied ±100%; prevalence and sensitivity/specificity rates were varied between 0 and 1; and compliance with follow-up testing and treatment was varied from 50% to 100%. Table 4 presents the threshold analyses for each of the three model populations. Model results were most sensitive to changes in the cost of HPV and Pap testing in the PapIIw population. For example, when the cost of HPV tests is increased from €40 to €42.6, managing women with repeat Pap becomes more cost effective than HPV triage for women with an initial PapIIw result. Likewise, when the cost of Pap tests decreases from €11.0 to €9.8, repeat Pap is the more cost-effective strategy. The threshold values presented reflect those values above or below which HPV triage ceases to be the most cost-effective management strategy. Results were also sensitive to the cost of follow-up visits in the PapIIw population. When costs drop below €13.8 for follow-up, repeat Pap is more cost effective.

In the PapIIw model, results were not sensitive to changes in the cost of treatment, Pap specificity,

Table 4 Threshold analyses for PapIIw, PapIII, and PapIIId. Threshold values reflect those values above or below which HPV triage would cease to be the most cost-effective strategy

Parameter	Base-case value	PapIIw	PapIII	PapIIId
Cost of HPV test	€40	€42.6	Not sensitive ^a	Not sensitive ^a
Cost of Pap test	€11.0	€9.8	Not sensitive ^a	Not sensitive ^a
Cost of treatment	€304.5	Not sensitive ^a	€85.1 ^c	€112.2 ^c
Cost of follow-up visit	€16.0	€13.8	Not sensitive ^a	Not sensitive ^a
Pap sensitivity	0.46	0.48	0.68	0.67
Pap specificity	0.89	Not sensitive ^a	Not sensitive ^a	Not sensitive ^a
HPV sensitivity	0.97	0.93	0.65	0.65
HPV specificity	0.79	0.75	0.59	0.55
Prevalence of CIN2+	0.08/0.34/0.13 ^b	Not sensitive ^a	0.78 ^c	0.78 ^c
Compliance with treatment/testing follow-up	100%	Not sensitive ^a	Not sensitive ^a	Not sensitive ^a

^a The model is not sensitive to changes in these inputs. Prevalence and sensitivity/specificity rates were varied between 0 and 1.0; cost inputs were varied $\pm 100\%$; compliance rates were varied from 50–100%

^b Values listed correspond to the prevalence of CIN2+ for PapIIw, PapIIId, and PapIII, respectively

^c Indicates scenarios for which managing women with immediate treatment is the most cost-effective strategy

compliance with follow-up, or to the prevalence of CIN2+. For PapIII and PapIIId, the model was not sensitive to test costs, the cost of or compliance with follow-up, or to Pap specificity. It was, however, somewhat sensitive to changes in the cost of treatment, as well as HPV and Pap sensitivity and HPV specificity. If the cost of treating CIN2+ were to decrease from €304.5 to less than €85.1 or €112.2 (for PapIII and PapIIId populations, respectively), then immediate treatment would be the most cost-effective management strategy for women with an initial Pap result of PapIII or PapIIId. Similarly, if CIN2+ prevalence were to exceed 0.78 in either of these populations (versus base case values of 0.134 and 0.343 for Pap III and IIId, respectively), it would be most cost effective to manage women through immediate treatment.

When compliance with follow-up was varied from 50% to 100%, both cost and effectiveness values decreased. However, in all three models, HPV remained the most cost-effective treatment. The relative cost effectiveness of HPV triage did not change in the PapIII and PapIIId models. In the case of PapIIw, the absolute cost effectiveness increased from €2,232 to €3,987 when the rate of compliance dropped to 50%.

Discussion

For each of the three model populations, HPV triage is the most cost-effective management strategy, i.e., the incremental cost-effectiveness ratio associated with HPV triage is less than the average cost-effectiveness ratio associated with repeat Pap and less than the incremental cost-effectiveness ratio associated with immediate treatment. Threshold analyses suggest that

the models are insensitive to changes in model inputs that fall within the range of values reported in the literature.

Our results are consistent with those found in studies conducted outside Germany. Kim et al. [20] constructed a computer-based mathematical model in the United States of America to compare four management strategies for a cytological result of atypical squamous cells of undetermined significance (ASCUS, Bethesda system; Munich classification equivalent of IIw/III): (1) immediate expert colposcopy; (2) HPV triage, which included expert colposcopy if high-risk HPV types were detected; (3) repeat cytology testing, which included follow-up cytological examination at 6 months and 12 months and referral for expert colposcopy if a repeat abnormal result occurred; (4) reclassifying ASCUS as normal, in which a cytological result of ASCUS is ignored. The study found the strategy of HPV triage was dominant (i.e., had both lower overall costs and improved outcomes) over repeat cervical cytology testing, regardless of screening interval or type of cervical cytology test. The study also found that HPV triage was much more cost effective than immediate referral for expert colposcopy. In a second study using this model to examine the cost effectiveness of HPV triage in the UK, The Netherlands, France, and Italy, Kim et al. found that HPV triage was more effective than each country's status quo screening policy, and each HPV triage scenario examined had an incremental cost-effectiveness ratio below \$13,000 per year of life saved [21]. Similar studies in the USA looking at management alternatives for ASCUS and atypical glandular cells of undetermined significance (AGCUS) also found HPV testing to be the most cost-effective option [22, 23]. Guyot et al. conducted a cost

comparison of two strategies for management of minor cytological abnormalities in the UK: (1) HPV triage; and (2) direct referral for expert colposcopy [24]. The study evaluated the condition of 133 women, 23 with persistent borderline changes and 110 with mild dyskaryosis (Munich classification equivalent of III/III_d) who were referred for colposcopy and HPV testing. The authors found that the strategy of HPV triage would be cost neutral at a price per HPV test of £34.37 (€50.50); at HPV reimbursement rates below this level, the strategy of HPV triage would be cost saving versus immediate expert colposcopy. Our results are also consistent with those of other studies that have shown HPV testing to be a cost-effective strategy for cervical cancer screening [25].

This analysis has a number of limitations. First, we were limited by the availability of published data addressing the specific aims of the model. Where precise data were lacking, expert opinion (correspondence with K.U. Petry and H. Ikenberg) was used to fill in the gaps in the literature. Data that were available were combined from a number of sources that varied in study design and patient populations. A second limitation involved the necessary simplification of potential strategies for managing women with atypical and abnormal cervical cancer screening results. Because various guidelines for managing women with atypical and abnormal Pap results suggest many different options in Germany, a great deal of variation exists among German practitioners. As a result, we relied heavily on the published literature, as well as on numerous consultations with German experts, to derive what we believe to be representative management strategies for women in Germany today. While we were unable to model the full range of possible alternatives, the strategies presented in the model reflect current practices to the best of our knowledge. Finally, the model was limited by the complex nature of cervical cancer itself, i.e., its natural history and its progression. Ideally, cost-effectiveness ratios are reported as cost per year of life saved (YLS) or cost per quality-adjusted life-year (QALY). However, because of the long-term nature of disease progression and the uncertainty associated with disease precursors, we chose to limit the analysis to 1 year. Thus, we report results in terms of cost per case of CIN2+ detected, acknowledging that the presence of high-grade lesions serves only as a proxy for potential cancers and ultimately years of life saved. Though a 1-year time frame is unable to capture the full impact of a given management strategy, it does help to inform more immediate decisions regarding the value of adopting new and promising technologies.

Considerable uncertainty regarding the longitudinal nature of HPV infection and cervical cancer still exists. As more data become available, the results presented here may be further refined.

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