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The Saudi Center for
Evidence Based Health Care

Cervical Cancer

Clinical Practice Guideline on the Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention

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Abbreviations

ASCUS	atypical squamous cells of undetermined significance
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
KSA	Kingdom of Saudi Arabia
LEEP	loop electrosurgical excision procedure (also LLETZ)
LLETZ	large loop excision of the transformation zone (also LEEP)
MoH	Ministry of Health
Pap test	Papanicolaou test (cytology-based method for cervical cancer screening)
QUADAS	QUality Assessment for Diagnostic Accuracy Studies
VIA	visual inspection with acetic acid
WHO	World Health Organization

Contents

Executive summary

Introduction

Cervical Intraepithelial Neoplasia grades 2 and 3 can progress to cervical cancer. It is anticipated that in Saudi Arabia, as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively. Thus screening and treatment of these precancerous lesions may be beneficial for preventing cervical cancer and related outcomes.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the 2013 WHO Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[2] We used this information to prepare the *evidence to recommendation tables* that served the guideline panel to follow a structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 4, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach. Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional ('guideline panel suggests…') and has explicit implications (see Table 1). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Table 1: Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Key questions

1. Should HPV test followed by colposcopy be preferred over VIA followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?
2. Should HPV test followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?
3. Should VIA followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?
4. Should Cryotherapy be preferred over CKC to treat women at risk of cervical cancer who tested positive after screening?
5. Should LEEP be preferred over CKC to treat women at risk of cervical cancer who tested positive after screening?
6. Should Cryotherapy be preferred over LEEP to treat women at risk of cervical cancer who tested positive after screening?

Recommendations

Recommendation 1:
The Ministry of Health of Saudi Arabia guideline panel recommends to use HPV test followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (strong recommendation, moderate quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

Remark:
In settings where colposcopy is not available, cytology is an alternative for women who tested positive in the HPV test (evidence not assessed).

Recommendation 2:
The Ministry of Health of Saudi Arabia guideline panel suggests to use HPV test followed by colposcopy over cytology followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

Remark:
In settings where colposcopy is not available, cytology is an alternative for women who tested positive in the HPV test (evidence not assessed).

Recommendation 3:
The Ministry of Health of Saudi Arabia guideline panel suggests to use cytology followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

Recommendation 4:
The Ministry of Health of Saudi Arabia guideline panel recommends to use cryotherapy over CKC to treat women at risk of cervical cancer who tested positive for CIN2+. (strong recommendation, very low quality evidence for health outcomes evidence)

Recommendation 5:
The Ministry of Health of Saudi Arabia guideline panel recommends to use LEEP over CKC to treat women at risk of cervical cancer who tested positive for CIN2+. (strong recommendation, very low quality evidence for health outcomes evidence)

Recommendation 6:
The Ministry of Health of Saudi Arabia guideline panel suggests to use cryotherapy over LEEP to treat women at risk of cervical cancer who tested positive for CIN2+. (conditional recommendation, very low quality evidence for health outcomes evidence)

Scope and purpose

The purpose of this document is to provide guidance about the population-based screening strategies to detect and treat cervical intraepithelial neoplasia (CIN) in order to reduce mortality and morbidity from cervical cancer. The target audience of these guidelines includes primary care physicians and gynaecologists in the Kingdom of Saudi Arabia. Specialists in medical oncology, other health care professionals, public health officers and policy makers may also benefit from these guidelines.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

Introduction

Cervical intraepithelial neoplasia is the premalignant transformation of squamous cells of the cervix.[4] If left untreated, the most severe forms of CIN (grade 2 or 3) could progress to cervical squamous cell carcinoma.[5] Therefore, screening and treating CIN2+ before it progresses to cervical cancer may be a beneficial intervention. These guidelines address questions regarding screening and treatment of CIN2+.

It is estimated that approximately 1–2% of women have CIN2+ each year worldwide. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year.[6] It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in the year 2025 are 309 and 117, respectively.[6]

Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the detailed methodology in a separate publication.[7]

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. The questions chosen by the guideline panel were adapted to make them applicable to the Saudi context. For all selected questions we updated existing systematic reviews that were used for the 2013 WHO Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (see **Appendix 2**).[2]

We assessed the quality of evidence using the system described by the GRADE working group.[8] Evidence regarding diagnostic accuracy of the screening strategies, and the effects of the screening and treatment strategies on critical and important health outcomes was sought in randomized controlled trials; how-

ever, no such studies were conducted and it was necessary to use clinical decision modelling techniques to combine studies that reported separately on these two aspects and obtain estimates of the effects of the different screening and treatment strategies.

Quality of evidence is classified as "high", "moderate", "low", or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of KSA MoH panel members we prepared the *evidence-to-recommendation* tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 4, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions about screening and treatment of precancerous lesions for cervical cancer prevention. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Key questions

The following is a list of the clinical questions selected by the KSA guideline panel and addressed in this guideline. For details on the process by which the questions were selected for this guideline please refer to the separate methodology publication.[7] Since the questions addressed in systematic reviews used for the WHO guidelines were targeted to low and middle-income countries, the questions were not completely applicable to the KSA setting, and thus were modified accordingly.

1. Should HPV test followed by colposcopy be preferred over VIA followed by colposcopy to screen for

CIN2+ in asymptomatic women at risk of cervical cancer?
2. Should HPV test followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?
3. Should VIA followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?
4. Should Cryotherapy be preferred over CKC to treat women at risk of cervical cancer who tested positive after screening?
5. Should LEEP be preferred over CKC to treat women at risk of cervical cancer who tested positive after screening?
6. Should Cryotherapy be preferred over LEEP to treat women at risk of cervical cancer who tested positive after screening?

Recommendations

I. Screening for precancerous lesions to prevent cervical cancer

Question 1: Should HPV test followed by colposcopy be preferred over VIA followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Summary of Findings:
No new studies were included in the systematic review. There was moderate quality evidence regarding the diagnostic accuracy of the screening strategies (5 cohort and cross-sectional studies, 8921 patients), and very low quality evidence regarding the effects of the screening strategies on health outcomes (decision making model combining studies providing information regarding diagnostic accuracy and health outcomes)

Benefits of HPV test followed by colposcopy compared to VIA followed by colposcopy:
Assuming a 2% probability of having CIN2+, HPV results in more true positives and less false negatives (see Table 1.1). Mortality due to cervical cancer, cervical cancer incidence, CIN2+ recurrence, and undetected CIN2+ rates are lower when patients are screened with HPV test (see Table 1.2). The guideline panel agreed that the benefits of HPV test over VIA are large.

Harms of HPV test followed by colposcopy compared to VIA followed by colposcopy:
HPV test followed by colposcopy results in less true negatives and more false positives (see Table 1.1). Adverse effects such as major bleeding, major and minor infections, and unnecessary treatments are slightly smaller after screening with VIA followed by colposcopy; however, the differences are not clinically significant for most of these outcomes (see Table 1.2). The guideline panel agreed that the harms of HPV test followed by colposcopy compared to VIA followed by colposcopy are small.
Values and Preferences:

The guideline panel agreed that most women would prefer to be screened with HPV test over VIA because the procedure takes less time to be administered. They also agreed that there is probably not important uncertainty and/or variability regarding women's values and preferences.

Resource Use:
The guideline panel agreed that even though there are extra resources needed to screen women with HPV test over VIA (considering resources needed for implementation), these resources are probably small and are worth the benefits. Once the program is implemented, HPV test would be cheaper.

Other Considerations:
Health inequities would be reduced if HPV test is implemented, and this would be an option acceptable to all key stakeholders. Since resources may be the only constraint for implementing HPV testing, and these are not perceived to be a problem in the KSA setting, HPV screening is an option feasible to implement. On the other hand, VIA is not an acceptable option nor it is feasible to imple-

ment, and therefore, health inequities would increase if it were implemented.

Implementation Considerations:
To implement this recommendation, the panel notes that resources such as equipment, maintenance, and trained professionals are needed. Also, there would be need to implement a system to transport samples from villages to main centers.

Research Priorities:
There is a need to have an accurate register of local data regarding the incidence and outcomes of CIN2+.

Recommendation 1:

The Ministry of Health of Saudi Arabia guideline panel recommends to use HPV test followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (strong recommendation, moderate quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

Remark:
In settings where colposcopy is not available, cytology is an alternative for women who tested positive in the HPV test (evidence not assessed).

Question 2: Should HPV test followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Summary of Findings:
No new studies were included in the systematic review. There was low quality evidence regarding the diagnostic accuracy of the screening strategies (11 cohort and cross-sectional studies, 39050 patients), and very low quality evidence regarding the effects of the screening strategies on health outcomes (decision making model combining studies providing information regarding diagnostic accuracy and health outcomes)

Benefits of HPV test followed by colposcopy compared to cytology followed by colposcopy:
Assuming a 2% probability of having CIN2+, HPV results in more true positives and less false negatives (see Table 2.1). Mortality due to cervical cancer, cervical cancer incidence, CIN2+ recurrence, and undetected CIN2+ rates are lower when patients are screened with HPV test (see Table 2.2). The guideline panel agreed that the benefits of HPV test followed by colposcopy over cytology followed by colposcopy are large.

Harms of HPV test followed by colposcopy compared to cytology followed by colposcopy:
HPV test followed by colposcopy results in less true negatives and more false positives (see Table 2.1). Adverse effects such as major bleeding, major and minor infections, and unnecessary treatments are slightly smaller after screening with cytology followed by colposcopy; however, the differences are not clinically significant for most of these outcomes (see Table 2.2). The guideline panel agreed that the harms of HPV test followed by colposcopy compared to cytology followed by colposcopy are small.

Values and Preferences:
The guideline panel agreed that most women would prefer to be screened with HPV test over VIA because the results of HPV test can be obtained faster, there is no need to undergo a specular exam and the procedure can be done by a nurse or the patient herself. They also agreed that there is probably not important uncertainty and/or variability regarding women's values and preferences.

Resource Use:
The guideline panel agreed that patients may incur in less costs if HPV testing is implemented, since there would be no need to visit a gynaecologist to collect the sample. Resources may be needed for implementation of an HPV testing program, but the benefits are worth the costs.

Other Considerations:
The fact that the screening could be done by health professionals other than the gynaecol-

ogists makes it easier to reach women in remote areas, which would reduce health inequities. HPV test would be an option acceptable to all key stakeholders. Since resources may be the only constraint for implementing HPV testing, and these are not perceived to be a problem in the KSA setting, HPV screening is an option feasible to implement.

Implementation Considerations:
To implement this recommendation, the panel notes that resources such as equipment, maintenance, and trained professionals are needed. Also, there would be need to implement a system to transport samples from villages to main centers.

Research Priorities:
There is a need to have an accurate register of local data regarding the incidence and outcomes of CIN2+.

Recommendation 2:

The Ministry of Health of Saudi Arabia guideline panel suggests to use HPV test followed by colposcopy over cytology followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

Remark:
In settings where colposcopy is not available, cytology is an alternative for women who tested positive in the HPV test (evidence not assessed).

Question 3: Should VIA followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Summary of Findings:
No new studies were included in the systematic review. There was low quality evidence regarding the diagnostic accuracy of the screening strategies (11 cohort and cross-sectional studies, 12089 patients), and very low quality evidence regarding the effects of the screening strategies on health outcomes (decision making model combining studies providing information regarding diagnostic accuracy and health outcomes)

Benefits of VIA followed by colposcopy compared to cytology followed by colposcopy:
The guideline panel agreed that the benefits of VIA over cytology are probably small, since there seems to be not clinically significant benefits when comparing both options.

Harms of VIA followed by colposcopy compared to cytology followed by colposcopy:
Assuming a 2% probability of having CIN2+, VIA followed by colposcopy results in less true negatives, less true positives, more false negatives and more false positives (see Table 3.1). Mortality due to cervical cancer, cervical cancer incidence, CIN2+ recurrence, and undetected CIN2+ rates are higher when patients are screened with VIA (see Table 3.2). Adverse effects such as major bleeding, major and minor infections, and unnecessary treatments are slightly smaller after screening with cytology followed by colposcopy; however, the differences are not clinically significant for most of these outcomes (see Table 2.2). The guideline panel agreed that the harms of VIA followed by colposcopy compared to cytology followed by colposcopy are large.

Values and Preferences:
This guideline panel agrees that women would consider as an advantage of VIA over cytology the time needed to get the results; however, when considering the procedure itself, cytology would be preferred. They also agreed that there is probably not important uncertainty and/or variability regarding women's values and preferences.

Resource Use:
The guideline panel agreed that VIA followed by colposcopy is cheaper than cytology followed by colposcopy; however, since there are not benefits of VIA followed by colposcopy over cytology followed by colposcopy, this is costs are not relevant.

Other Considerations:
VIA is not currently implemented in Saudi Arabia. All physicians would need to be trained to perform this screening test, which makes it an option not feasible to implement and would probably cause health inequities in terms of people who will have access to trained physicians. Therefore, this would not be an acceptable option from key stakeholders.

Implementation Considerations:
There is a need to expand the structure to perform cytology in a large scale in KSA.

Research Priorities:
There is a need to have an accurate register of local data regarding the incidence and outcomes of CIN2+.

Recommendation 3:

The Ministry of Health of Saudi Arabia guideline panel suggests to use cytology followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

II. Treatment of CIN2+ lesions for preventing cervical cancer in women who tested positive after screening

Question 4: Should Cryotherapy be preferred over CKC to treat women at risk of cervical cancer who tested positive after screening?

Summary of Findings:
No new studies were included in the systematic review. There was very low quality evidence regarding the effects of the screening strategies on health outcomes (decision making model combining studies providing information regarding diagnostic accuracy and health outcomes)

Benefits of cryotherapy compared to CKC:
After treatment with cryotherapy, there is a slightly higher mortality, cervical cancer incidence and CIN2+ recurrence rate; however, the guideline panel considered that the differences were not clinically significant (see tables 1.2, 2.2 and 3.2).

Harms of cryotherapy compared to CKC: After treatment with cryotherapy, there is a lower rate of major bleeding, major and minor infections and premature deliveries, irrespective of the screening strategy used (see tables 1.2, 2.2 and 3.2). The difference in these outcomes was considered to be clinically important, and thus the guideline panel agreed that the benefits of cryotherapy compared to CKC probably outweigh the harms.

Values and Preferences:
The guideline panel agreed that most women would prefer to undergo treatment with cryotherapy because it is a procedure that can be done as outpatient. The only disadvantage is an increase in secretions after treatment with cryotherapy, which may lead to need further control visits. They also agreed that there is probably not uncertainty and variability in these values and preferences.

Resource Use:
The guideline panel agreed that cryotherapy would be cheaper than CKC, and thus it would be a cost saving alternative.
Other Considerations:
The guideline panel agreed that inequities would be reduced if cryotherapy were implemented and that this is an option acceptable to all key stakeholders. Both options would be feasible to implement.

Research Priorities:
There is a need for research regarding health outcomes after treatment with these options.

Recommendation 4:

The Ministry of Health of Saudi Arabia guideline panel recommends to use cryotherapy over CKC to treat women at risk of cervical cancer who tested positive for CIN2+. (strong recommendation, very low quality evidence for health outcomes evidence)

Question 5: Should LEEP be preferred over CKC to treat women at risk of cervical cancer who tested positive after screening?

Summary of Findings:
No new studies were included in the systematic review. There was very low quality evidence regarding the effects of the screening strategies on health outcomes (decision making model combining studies providing information regarding diagnostic accuracy and health outcomes)

Benefits of LEEP compared to CKC:
After treatment with LEEP, there is a slightly higher mortality, cervical cancer incidence and CIN2+ recurrence rate; however, the guideline panel considered that the differences were not clinically significant (see tables 1.2, 2.2 and 3.2).

Harms of LEEP compared to CKC:
After treatment with cryotherapy, there is a lower rate of major bleeding, minor infections and premature deliveries; and a higher rate of major infections irrespective of the screening strategy used (see tables 1.2, 2.2 and 3.2). The difference in these outcomes was considered to be clinically important, and thus
the guideline panel agreed that the benefits of LEEP compared to CKC probably outweigh the harms.

Values and Preferences:
The guideline panel agreed that most women would prefer to receive treatment with LEEP over CKC due to the lower rate of complications and the possibility of performing the procedure in an outpatient clinic; and that there is probably no uncertainty and variability in these values and preferences.

Resource Use:
The guideline panel agreed that LEEP would be cheaper than CKC, and thus it would be a cost saving alternative.

Other Considerations:
The guideline panel agreed that inequities would be reduced if cryotherapy were implemented and that this is an option acceptable to all key stakeholders. Both options would be feasible to implement.

Research Priorities:
There is need for research regarding health outcomes after treatment with these options.

Recommendation 5:

> The Ministry of Health of Saudi Arabia guideline panel recommends to use LEEP over CKC to treat women at risk of cervical cancer who tested positive for CIN2+ (strong recommendation, very low quality evidence for health outcomes evidence)

Question 6: Should Cryotherapy be preferred over LEEP to treat women at risk of cervical cancer who tested positive after screening?

Summary of Findings:
No new studies were included in the systematic review. There was very low quality evidence regarding the effects of the screening strategies on health outcomes (decision making model combining studies providing information regarding diagnostic accuracy and health outcomes)

Benefits of cryotherapy compared to LEEP:
There are no differences in benefits after treatment with cryotherapy compared to LEEP (see tables 1.2, 2.2 and 3.2).

Harms of cryotherapy compared to LEEP:
After treatment with cryotherapy, there is a lower rate of major bleeding and **major** infections. There are not clinically significant differences in premature deliveries and minor infections irrespective of the screening strategy used (see tables 1.2, 2.2 and 3.2). The guideline panel agreed that the benefits of cryotherapy compared to LEEP probably outweigh the harms.

Values and Preferences:
The guideline panel agrees that most women would prefer to undergo treatment with cryotherapy over LEEP; and that there is probably no uncertainty and variability in these values and preferences.

Resource Use:
The guideline panel agreed that cryotherapy would be cheaper than LEEP, and thus it would be a cost saving alternative.

Other Considerations:
The guideline panel agreed that inequities would be reduced if cryotherapy were implemented and that this is an option acceptable to all key stakeholders. Both options would be feasible to implement.

Implementation Considerations:
LEEP is a valid alternative particularly in settings where there are experienced physicians and the equipment is available
Research Priorities:
There is need for research regarding health outcomes after treatment with these options.

Recommendation 6:

The Ministry of Health of Saudi Arabia guideline panel suggests to use cryotherapy over LEEP to treat women at risk of cervical cancer who tested positive for CIN2+. (conditional recommendation, very low quality evidence for health outcomes evidence)

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Appendices

1. Evidence-to-Recommendation Tables and Evidence Profiles
2. Search Strategies and Results

Appendix 1: Evidence-to-Recommendation Tables and Evidence Profiles

Evidence to recommendation framework 1

Should HPV test followed by colposcopy be preferred over VIA followed by colposcopy to screen for CIN 2+ in asymptomatic women at risk of cervical cancer?

Population: Women at risk of cervical cancer
Option: HPV test followed by colposcopy
Comparison: VIA followed by colposcopy
Setting: Community
Perspective: Public Health/ Policy making (Ministry of Health)

Background: This is an adaptation of the "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention". The objective of this adaptation is to make the recommendations applicable to the context of Saudi Arabia. The following difference/remark was detected with respect to the original guidelines question and of relevance to this recommendation question: The majority of women would undergo histological confirmation, and thus all screening strategies have to be followed by colposcopy.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is estimated that approximately 1–2% of women have CIN2+ each year. If left untreated, CIN2+ can progress to cervical cancer. In Saudi Arabia. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year (source: Globocan 2008). It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively.	Guideline panel considerations: - Although cervical cancer used to be a rare condition, its incidence has increased over the last 10 years - There is an official national register (from 2005 to 2009, from which the globocan statistics collected information), but it may not be accurate since there may be underreporting issues. - Even though the incidence is not very high, mortality associated to cervical cancer is high, which makes this problem a priority

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	☐ No included studies ☒ Very low ☐ Low ☒ Moderate ☐ High		The panel revised and agreed on the outcome ranking and judgments. Evidence from qualitative studies suggests women may fear screening and may have a high level of anxiety related to colposcopy or treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. This evidence comes from developing countries. The panel of the original guideline considered that this information is applicable to most women in low and middle-income countries. The guideline panel also agreed that women would be more likely to prefer HPV testing over VIA since
Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ No important uncertainty or variability ☐ No known undesirable outcomes		
Are the desirable anticipated effects large?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies		
Are the undesirable anticipated effects small?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies		
Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies		

Outcome	Relative importance	Certainty of the evidence
Mortality	CRITICAL	⊕⊕⊕⊖ moderate for the diagnostic accuracy of HPV and VIA ⊕⊖⊖⊖ very low for the effects of treatment and the natural progression of CIN
Cervical cancer incidence	CRITICAL	
CIN2+ recurrence	IMPORTANT	
Undetected CIN2+	CRITICAL	
Major bleeding	IMPORTANT	
Premature delivery	IMPORTANT	
Infertility	IMPORTANT	
Major infections	IMPORTANT	
Minor infections	NOT IMPORTANT	
Unnecessary treatment	IMPORTANT	

Summary of findings: *See tables 1.1 and 1.2*

- *HPV test has 5/1000 more true positives*
- *HPV test has 0-17/1000 less true negatinves*
- *HPV test has 0-17/1000 more false positives*
- *HPV test has 5/1000 less false negatives*
- *VIA results in higher mortality, cervical incidence and CIN2+ recurrence*

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				the former intervention requires less time to be administered.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	No evidence found	The panel thought that the resources required to run the screening program with HPV test, once everything is in place, would probably be small (compared to the resources needed to run a VIA screening program) However, the resources needed to implement the HPV test screening strategy may be high If both, implementation and running costs are compared, VIA would be cheaper
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	No evidence found	The panel of the original guideline agreed that HPV testing is resource-dependent. Where HPV testing is available, affordable and implementable, the overall net benefit over VIA is worth the resources. But where not available, HPV test may not be worth the benefits. This guideline panel agreed that the benefits are worth the costs.
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ☒ ***Varies*** ☐	No evidence found	According to the panel, the gap on inequities will be reduced if HPV test is introduced as a screening strategy, since it would be easier to reach all women in different geographic areas, due to the nature of the test procedure (easiness to collect samples, particularly in remote areas). In contrast, inequities would probably increase if VIA were implemented, due to the lack of trained physicians and the difficulties to reach one of the trained physicians.
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	No evidence found	The panel agrees that HPV testing is an acceptable option from all perspectives, as opposed to VIA, which would not be an acceptable option.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | *Varies* ☐	In Saudi Arabia, most centers are already using conventional cytology for opportunistic screening for cervical cancer. Recently, some centers adopted the used of liquid based cytology as a method of screening which help to do HPV testing (Sait 2012)	The panel agrees that if resources are in place for implementation, HPV is an option feasible to implement. Also, resources are not perceived as a big barrier. In places where already implemented, it is running well. In addition, VIA would not be an option feasible to implement since none health professional is familiar with the intervention,

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

Type of recommendation	We recommend against offering this option ☐	We suggest not offering this option ☐	We suggest offering this option ☐	We recommend offering this option ☒

Recommendation (text)

The Ministry of Health of Saudi Arabia guideline panel recommends to use HPV test followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer (strong recommendation, moderate quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)

Justification

Even though the quality of the evidence was very low for the evidence regarding the health outcomes, it was moderate for the diagnostic test accuracy properties. The panel agreed that there are potentially large benefits and small harms (despite the lower confidence in the estimates of effects), and that patients' values and preferences had little variation. A high weight was given to these judgments, together with the potential reduction of health inequities, and no issues regarding acceptability and feasibility. Also, a high weight was given to the fact none health professional in KSA is trained to perform VIA.

Subgroup considerations

In settings where colposcopy is not available, cytology is an alternative for women who tested positive in the HPV test (evidence not assessed).

Implementation considerations	To implement this recommendation, the panel notes that resources such as equipment, maintenance, and trained professionals are needed. Also, there would be need to implement a system to transport samples from villages to main centers.
Monitoring and evaluation	-
Research priorities	There is need to have an accurate register of local data regarding the incidence and outcomes of CIN2+

Evidence profile 1.1: Diagnostic test accuracy (DTA) evidence profile: HPV test followed by colposcopy compared to VIA followed by colposcopy

Author(s): RBP, JB, NS, RM
Date: 2013-11-28

Outcome	No. of studies (No. of patients)*	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by colposcopy**	VIA followed by colposcopy**	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies[9999999]	None [1]	None	None [2]	None	Undetected	⊕⊕⊕⊕ high	18-19	13-14	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[1]	None	Serious [2]	None[3]	Undetected	⊕⊕⊕⊖ moderate	889-980	906-980	CRITICAL
TN absolute difference									0-17 less		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[1]	None	Serious [2]	None[3]	Undetected	⊕⊕⊕⊖ moderate	0-91	0-74	CRITICAL
FP absolute difference									17 more		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None [1]	None	None [2]	None	Undetected	⊕⊕⊕⊕ high	1-2	6-7	CRITICAL
FN absolute difference									5 less		

Diagnostic test accuracy

Pooled sensitivity HPV test	95% (95% CI: 84 to 98)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)	Pooled sensitivity colposcopic impresssion	95% (95% CI: 86 to 98)
Pooled specificity HPV test	84% (95% CI: 72 to 91)	Pooled specificity cytology VIA	87% (95% CI: 79 to 92)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference Standard: Colposcopy with biopsy when indicated)

Footnotes:

***** This is the number of studies that assessed data for HPV test and cytology.

** The range represents the effect when the colposcopy is followed by impression or biopsy

[1] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. Downgraded one level in context of other factors, in particular indirectness.

[2] Estimates of HPV test, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. Downgraded one level in the context of other factors, in particular imprecision.

[3] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

[4] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

1.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by colposcopy compared to VIA followed by colposcopy

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)*						
	HPV →colp +/– CKC	HPV →colp +/– LEEP	HPV →colp +/– cryo	VIA→colp +/– CKC	VIA→colp +/–LEEP	VIA→colp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20-32	31-42	31-42	83-91	91-99	91-99	250
Cervical cancer incidence[2]	28-44	43-58	43-58	116-128	127-138	127-138	350
CIN2+ recurrence[3]	1088-1704	1667-2263	1667-2263	4458-4905	4884-5311	4885-5311	13 400
Undetected CIN2+ (FN)	1000-2000			6000-7000			
Major bleeding[4]	163-937	43-246	7-37	118-745	31-196	5-29	0
Premature delivery[5]	523-631	508-546	512-568	517-605	506-537	509-568	500
Infertility[6]	-	-	-	-	-	-	-
Major infections[7]	17-97	24-140	3-15	12-77	18-111	2-12	0
Minor infections[8]	178-1022	115-658	123-706	129-813	83-523	89-562	0
Unnecessarily treated (FP)	0-91000			0-74000			-
Cancer found at first-time screening[9]	2454			3168			0

Footnotes:

The colours in the table: In each GRADE evidence table, colour-coding is used to highlight the 'desirability' of the effects for that outcome relative to other outcomes. The continuum runs from light green (desirable) through yellow and orange to red (least desirable).

The numbers in the table are based on

* CIN2+ pretest probability 2%
* HPV test: pooled sensitivity 95% (95% CI: 84 to 98), pooled specificity 84% (95% CI 72 to 91)
* VIA: pooled sensitivity 69% (95% CI: 54 to 81), pooled specificity 87% (95% CI 79 to 92)
* Colposcopic impression: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)

* The overall QoE for each of these outcomes is very low ⊕⊖⊖⊖. Our lack of confidence in these effect estimates stems mainly from very low-quality evidence for treatment effects and natural progression/history data.
The numbers of events are presented as ranges. The lower value was obtained when colposcopy followed by biopsy data was used, whereas the higher value was obtained when colposcopy followed by impression data was used

1 We assume no mortality from cervical cancer in true negative (TN) and false positive (FP). To calculate the mortality from cervical cancer, we assumed 250 deaths per 350 women with cervical cancer. These numbers are based on Eastern Africa age-standardized rates of cervical cancer and mortality provided by WHO at http://globocan.iarc.fr/, accessed 30 October 2012).
2 We assume no cervical cancer in TN or FP. To calculate cervical cancer incidence in women with persistent CIN2+, we assumed 350 cervical cancers per 14 000 women who have persistent CIN2+ (i.e. FN). This incidence is based on Eastern Africa age-standardized rate of cervical cancer of 350 cervical cancers per 1 000 000 women, of whom 2% have CIN2+ (20 000 women with CIN2+, and a subsequent 30% regression for a total of 14 000 with persistent CIN2+). These data are available from WHO at http://globocan.iarc.fr/, accessed 30 October 2012).
3 We assume no CIN2+ in TN and FP. Our calculations in the model are based on 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.
4 We assumed major bleed would be 0 in TN and FN as they were not treated. We assumed 0.000339 of the population treated with cryotherapy, 0.002257 with LEEP, and 0.001705 with CKC, based on pooled proportions in observational studies with no independent controls, will have major bleeding.
5 We assumed 5% population risk of premature delivery in 1% women who become pregnant. Based on pooled meta-analysis of controlled observational studies, 0.001125 of the population treated with cryotherapy, 0.000925 with LEEP, and 0.001705 of the population treated with CKC will have premature delivery.
6 We did not identify any data about the risk of infertility after treatment for CIN2+.
7We assumed major infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control 0.000135 of the population treated with cryotherapy 0.001279 with LEEP, and 0.000888 with CKC will have major infection.
8 We assumed minor infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.006473 of the population treated with cryotherapy, 0.006027 with LEEP, and 0.009368 with CKC will have minor infection.
9 Cancers detected at first-time screening calculated from Sankaranarayanan et al. (2005). Numbers for single screening tests were calculated as 'screen-detected' cancers in women who participated in the screening programme; and numbers for test with colposcopy were calculated as 'screen detected' plus 'clinically detected' cancers. For a sequence of tests (e.g. HPV test followed by VIA), the greater number of cancers detected between tests was used. No cancers would be found in the 'no screen' group. This is not the annual incidence of cervical cancer (which is shown in a row above). It represents the cumulative rate of cancer development before screening started (i.e. the prevalence of cancer at the time when screening is conducted).
10 'No screen' numbers were calculated using the same assumptions above for FN, with the exception of premature delivery which was baseline risk in the population.

References included in the meta-analysis of diagnostic test accuracy

1. Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic Oncology*, 2001, 83(2):439–444.
    a. Pan Q et al. A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma a cross-sectional, comparative study. *Acta Cytologica*, 2003, 47(1):45–50.
2. De Vuyst H et al. Comparison of Pap smear, visual inspection with acetic acid, human papillomavirus DNA-PCR testing and cervicography. *International Journal of Gynecology & Obstetrics*, 2005, 89(2):120–126.
3. Qiao YL et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncology*, 2008, 9(10):929–936.
4. Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.
5. Sodhani P et al. Test characteristics of various screening modalities for cervical cancer: a feasibility study to develop an alternative strategy for resource-limited settings. *Cytopathology*, 2006, 17(6):348–352.

References to studies included for diagnostic test accuracy of colposcopic impression

1. Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic Oncology*, 2001, 83(2):439–444.
2. Cantor SB et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. *Obstetrics & Gynecology*, 2008, 111(1):7–14.
3. Cremer ML et al. Digital assessment of the reproductive tract versus colposcopy for directing biopsies in women with abnormal Pap smears. *Journal of Lower Genital Tract Disease*, 2010, 14(1):5–10.
4. Cristoforoni PM et al. Computerized colposcopy: results of a pilot study and analysis of its clinical relevance. *Obstetrics & Gynecology*, 1995, 85(6):1011–1016.
5. Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. *Journal of the Turkish German Gynecology Association*, 2009, 10(4):205–207.
6. Ferris DG, Miller MD. Colposcopic accuracy in a residency training program: defining competency and proficiency. *Journal of Family Practice*, 1993, 36(5):515–520.
7. Homesley HD, Jobson VW, Reish RL. Use of colposcopically directed, four-quadrant cervical biopsy by the colposcopy trainee. *Journal of Reproductive Medicine*, 1984, 29(5):311–316.
8. Jones DE et al. Evaluation of the atypical Pap smear. *American Journal of Obstetrics & Gynecology*, 1987, 157(3):544–549.
9. Kierkegaard O et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetricia et Gynecologica Scandinavica*, 1994, 73(8):648–651.
10. Mousavi AS et al. A prospective study to evaluate the correlation between Reid colposcopic index impression and biopsy histology. *Journal of Lower Genital Tract Disease*, 2007, 11(3):147–150.
11. Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: Is VIA superseding Pap smear? *Journal of SAFOG*, 2011, 3(3):131–134.

Evidence to recommendation framework 2

Should HPV test followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Population: Women at risk of cervical cancer
Option: HPV test followed by colposcopy
***Comparison*:** Cytology followed by colposcopy
Setting: Community
Perspective: Public Health/ Policy making (Ministry of Health)

Background: This is an adaptation of the "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention". The objective of this adaptation is to make the recommendations applicable to the context of Saudi Arabia. The following differences/remarks were detected with respect to the original guidelines question: 1. The majority of women would undergo histological confirmation, and thus all screening strategies have to be followed by colposcopy, 2. The cut-off point for a cytology test is ASC-US (atypical squamous cells of undetermined significance)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is estimated that approximately 1–2% of women have CIN2+ each year. If left untreated, CIN2+ can progress to cervical cancer. In Saudi Arabia. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year (source: Globocan 2008). It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively.	Guideline panel thoughts: - Although cervical cancer used to be a rare condition, its incidence has increased over the last 10 years - There is an official national register (from 2005 to 2009, from which the globocan statistics collected information), but it may not be accurate since there may be underreporting issues. - Even though the incidence is not very high, mortality associated to cervical cancer is high, which makes this problem a priority

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☒ | Low ☐ | Moderate ☐ | High ☐		The panel revised and agreed on the outcomes ranking and judgments.
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☐ | No important uncertainty or variability ☒ | No known undesirable outcomes ☐		Evidence from qualitative studies suggests women may fear screening and may have a high level of anxiety related to colposcopy or treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. In addition, evidence from controlled trials showed that women find treatment by cryotherapy and LEEP acceptable, and are satisfied with a screen-and-treat approach. This evidence comes from developing countries. The panel of the original guideline considered that this information is applicable to most women in low and middle income countries.
Are the desirable anticipated effects large?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐		
Are the undesirable anticipated effects small?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐		
Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐		The guideline panel be-

Outcome	Relative importance	Certainty of the evidence
Mortality	CRITICAL	⊕⊕⊖⊖ low for the diagnostic accuracy of HPV test and cy tology ⊕⊖⊖⊖ very low for the effects of treatment and natural progression of CIN
Cervical cancer incidence	CRITICAL	
CIN2+ recurrence	IMPORTANT	
Undetected CIN2+	CRITICAL	
Major bleeding	IMPORTANT	
Premature delivery	IMPORTANT	
Infertility	IMPORTANT	
Major infections	IMPORTANT	
Minor infections	NOT IMPORTANT	
Unnecessary treatment	IMPORTANT	

Summary of findings: *See tables 2.1 and 2.2*

- *HPV test has 5/1000 more true positives*
- *HPV test has 0-29/1000 less true negatinves*
- *HPV test has 0-29/1000 more false positives*
- *HPV test has 5/1000 less false negatives*
- *Cytology results in higher mortality, cervical incidence and CIN2+ recurrence*
- *The incidence of major infections is similar after both screening strategies.*
- *The incidence of minor infections is similar across screening strategies*

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				lieves women may prefer to undergo screening with HPV test over cytology because: - The results from the test can be obtained faster - There is no need to undergo a specular exam - The procedure can be done by a nurse, or sometimes even by the patient herself

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	No evidence found	The panel of the original guideline agreed that there may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. However, in countries where an appropriate/high-quality screening strategy with cytology exists, resources would be required to change over to HPV test. Even though there are no official costs estimates, this guideline panel agreed that patients may incur in less costs if HPV testing is implemented, since there would be no need to visit a gynaecologist to collect the sample.
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	No evidence found	The panel of the original guideline agreed that HPV testing is resource-dependent. Where HPV testing is available, affordable and implementable, the overall net benefit over VIA is worth the resources. But where not available, HPV test may not be worth the benefits. This guideline panel agreed that the benefits are worth the costs.
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ☒ ***Varies*** ☐	No evidence found	According to the panel, the gap on inequities will be reduced if HPV test is introduced as a screening strategy, since it would be easier to reach all women in different geographic areas, due to the nature of the test procedure (easiness to collect samples, particularly in remote areas).
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	No evidence found	The panel agrees that HPV testing is an acceptable option from all perspectives.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	In Saudi Arabia, most centers are already using conventional cytology for opportunistic screening for cervical cancer. Recently, some centers adopted the used of liquid based cytology as a method of screening which help to do HPV testing (Sait 2012)	The panel agrees that if resources are in place for implementation, HPV is an option feasible to implement. Also, resources are not perceived as a big barrier. In places where already implemented, it is running well.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel suggests to use HPV test followed by colposcopy over cytology followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)
Justification	The quality of the evidence was low for the evidence regarding the diagnostic test accuracy of the options, and very low for the evidence regarding the health outcomes. The panel agreed that there are potentially large benefits and small harms (despite the lower confidence in the estimates of effects), and that patients' values and preferences had little variation. These judgements were combined with the potential reduction of health inequities, and no issues regarding acceptability and feasibility.
Subgroup considerations	In settings where colposcopy is not available, cytology is an alternative for women who tested positive in the HPV test (evidence not assessed).
Implementation considerations	To implement this recommendation, the panel notes that resources such as equipment, maintenance, and trained professionals are needed. Also, there would be need to implement a system to transport samples from villages to main centers.
Monitoring and evaluation	-
Research priorities	There is need to have an accurate register of local data regarding the incidence and outcomes of CIN2+

Evidence profile: 2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by colposcopy compared to cytology (ASCUS) followed by colposcopy

Author(s): RBP, JB, NS, RM

Date: 2013-11-28

Outcome	No. of studies (No. of patients)*	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by colposcopy**	Cytology followed by colposcopy**	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies[10101010101010]	Serious [1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	18-19	13-14	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	923-980	952-980	CRITICAL
TN absolute difference									0-29 less		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	0-57	0-28	CRITICAL
FP absolute difference									0-29 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	1-2	6-7	CRITICAL
FN absolute difference									5 less		

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology **(ASCUS)**	70% (95% CI: 57 to 81)	Pooled sensitivity colposcopic impresssion	95% (95% CI: 86 to 98)

Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity cytology **(AS-CUS)**	95% (95% CI: 92 to 97)	Pooled specificity col-poscopic impression	42% (95% CI: 26 to 61)

(Reference Standard: Colposcopy with biopsy when indicated)

Footnotes:

***** This is the number of studies that assessed data for HPV test and cytology.

** The range represents the effect when the colposcopy is followed by impression or biopsy

[1] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. Downgraded one level in context of other factors, in particular indirectness.

[2] Estimates of HPV test, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. Downgraded one level in context of other factors, in particular imprecision.

[3] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

[4] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

2.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by colposcopy compared to cytology (ASCUS) followed by colposcopy

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)*						
	HPV →colp +/– CKC	HPV →colp +/– LEEP	HPV →colp +/– cryo	Cyto→colp +/– CKC	Cyto→colp +/–LEEP	Cyto→colp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	22-34	33-44	33-44	81-89	88-96	88-96	250
Cervical cancer incidence[2]	31-47	46-61	46-61	113-125	124-135	124-135	350
CIN2+ recurrence[3]	1218-1827	1800-2380	1800-2380	4328-4782	4762-5194	4762-5194	13 400
Undetected CIN2+ (FN)	1000-2000			6000-7000			
Major bleeding[4]	161-641	42-169	6-25	120-358	32-94	5-14	0
Premature delivery[5]	523-590	508-532	512-547	517-550	506-518	509-526	500
Infertility[6]	-	-	-	-	-	-	-
Major infections[7]	17-66	24-96	3-10	12-37	18-53	2-6	0
Minor infections[8]	176-700	113-450	122-484	131-391	84-251	91-270	0
Unnecessarily treated (FP)	0-57000			0-28 000			-
Cancer found at first-time screening[9]	2454			4794			0

Footnotes:
The colours in the table: In each GRADE evidence table, colour-coding is used to highlight the 'desirability' of the effects for that outcome relative to other outcomes. The continuum runs from light green (desirable) through yellow and orange to red (least desirable).
The numbers in the table are based on
* CIN2+ pretest probability 2%
* HPV test: pooled sensitivity 94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
* Cytology (ASCUS): pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
* Colposcopic impression: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
* The overall QoE for each of these outcomes is very low ⊕⊖⊖⊖. Our lack of confidence in these effect estimates stems mainly from very low-quality evidence for treatment effects and natural progression/history data.
The numbers of events are presented as ranges. The lower value was obtained when colposcopy followed by biopsy data was used, whereas the higher value was obtained when colposcopy followed by impression data was used

[1] We assume no mortality from cervical cancer in true negative (TN) and false positive (FP). To calculate the mortality from cervical cancer, we assumed 250 deaths per 350 women with cervical cancer. These numbers are based on Eastern Africa age-standardized rates of cervical cancer and mortality provided by WHO at http://globocan.iarc.fr/, accessed 30 October 2012).
[2] We assume no cervical cancer in TN or FP. To calculate cervical cancer incidence in women with persistent CIN2+, we assumed 350 cervical cancers per 14 000 women who have persistent CIN2+ (i.e. FN). This incidence is based on Eastern Africa age-standardized rate of cervical cancer of 350 cervical cancers per 1 000 000 women, of whom 2% have CIN2+ (20 000 women with CIN2+, and a subsequent 30% regression for a total of 14 000 with persistent CIN2+). These data are available from WHO at http://globocan.iarc.fr/, accessed 30 October 2012).
[3] We assume no CIN2+ in TN and FP. Our calculations in the model are based on 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.
[4] We assumed major bleed would be 0 in TN and FN as they were not treated. We assumed 0.000339 of the population treated with cryotherapy, 0.002257 with LEEP, and 0.001705 with CKC, based on pooled proportions in observational studies with no independent controls, will have major bleeding.
[5] We assumed 5% population risk of premature delivery in 1% women who become pregnant. Based on pooled meta-analysis of controlled observational studies, 0.001125 of the population treated with cryotherapy, 0.000925 with LEEP, and 0.001705 of the population treated with CKC will have premature delivery.
[6] We did not identify any data about the risk of infertility after treatment for CIN2+.
[7] We assumed major infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control 0.000135 of the population treated with cryotherapy 0.001279 with LEEP, and 0.000888 with CKC will have major infection.
[8] We assumed minor infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.006473 of the population treated with cryotherapy, 0.006027 with LEEP, and 0.009368 with CKC will have minor infection.

References to studies included in meta-analysis of diagnostic test accuracy

1. Agorastos T et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecologic Oncology*, 2005, 96(3):714–720.
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11. Qiao YL et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncology*, 2008, 9(10):929–936.

References to studies included for diagnostic test accuracy of colposcopic impression

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Evidence to recommendation framework 3

Should VIA followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN 2+ in asymptomatic women at risk of cervical cancer?

Population: Women at risk of cervical cancer
Option: VIA followed by colposcopy
Comparison: Cytology followed by colposcopy
Treatment options: Cryotherapy, LEEP and CKC
Setting: Community
Perspective: Public Health/ Policy making (Ministry of Health)

Background: This is an adaptation of the "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention". The objective of this adaptation is to make the recommendations applicable to the context of Saudi Arabia. The following differences/remarks were detected with respect to the original guidelines question: 1. The majority of women would undergo histological confirmation, and thus all screening strategies have to be followed by colposcopy, 2. The cut-off point for a cytology test is ASC-US (atypical squamous cells of undetermined significance)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	It is estimated that approximately 1–2% of women have CIN2+ each year. If left untreated, CIN2+ can progress to cervical cancer. In Saudi Arabia. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year (source: Globocan 2008). It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively.	Guideline panel thoughts: - Although cervical cancer used to be a rare condition, its incidence has increased over the last 10 years - There is an official national register (from 2005 to 2009, from which the globocan statistics collected information), but it may not be accurate since there may be underreporting issues. - Even though the incidence is not very high, mortality associated to cervical cancer is high, which makes this problem a priority

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☒ | *Low* ☐ | *Moderate* ☐ | *High* ☐		
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☒ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	CRITICAL	⊕⊕⊖⊖ low for the diagnostic accuracy of VIA and cytology
Cervical cancer incidence	CRITICAL	
CIN2+ recurrence	CRITICAL	
Undetected CIN2+	CRITICAL	
Major bleeding	CRITICAL	⊕⊖⊖⊖ very low for the effects of treatment and the natural progression of CIN
Premature delivery	IMPORTANT	
Infertility	IMPORTANT	
Major infections	CRITICAL	
Minor infections	IMPORTANT	
Unnecessary treatment	IMPORTANT	

Summary of findings: *See tables 3.1 and 3.2*

- *VIA has 1-2/1000 less true positives*
- *VIA has 0-34/1000 less true negatinves*
- *VIA has 0-34/1000 more false positives*
- *VIA has 1-2/1000 less false negatives*
- *VIA results in higher mortality, cervical incidence and CIN2+ recurrence*
- *The incidence of minor infections is similar across screening strategies*

The panel revised and agreed on the outcomes ranking and judgments.

Evidence from qualitative studies suggests women may fear screening and may have a high level of anxiety related to colposcopy or treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. In addition, evidence from controlled trials showed that women find treatment by cryotherapy and LEEP acceptable, and are satisfied with a screen-and-treat approach. This evidence comes from developing countries. The panel of the original guideline considered that this information is applicable to most women in low and middle income countries.

This guideline panel agrees that women would consider as an advantage of VIA over cytology the time needed to get the results; however, when considering the procedure itself, cytology would be preferred.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Although there are not official cost estimations, the guideline panel agrees that VIA would be cheaper than cytology.
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	The panel of the original guideline agreed that fewer resources are required for VIA. There may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. This guideline panels sees no additional effectiveness of VIA compared to cytology, and thus the fact that VIA may be cheaper is not important (resources are not considered a big barrier)
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☒ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐	No evidence found	VIA is not currently implemented in Saudi Arabia. The guideline panel agrees that all physicians would need to be trained to perform this screening test, which will likely cause inequities in terms of people who will have access to trained physicians.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	The guideline panel agrees that this is an option not acceptable from the physicians' perspective, because they would need to be trained to perform a test which they perceive to be inferior to the alternatives.
FEASIBILITY	Is the option feasible to implement?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	In Saudi Arabia, most centers are already using conventional cytology for opportunistic screening for cervical cancer. (Sait 2012)	The guideline panel agrees that there are no physicians trained to perform VIA in KSA, and that it is not possible to train enough people to implement this test.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☒	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☒	☐	☐

Recommendation (text)	The KSA MoH guideline panel suggests to use cytology followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence)
Justification	The quality of the evidence was low for the evidence regarding the diagnostic test accuracy of the options, and very low for the evidence regarding the health outcomes. The panel agreed that there no extra benefits of VIA over cytology and that women were more likely to prefer cytology. These judgements were combined with all the barriers to implement VIA as an option and the issues with acceptability and potential increase in inequities.
Subgroup considerations	
Implementation considerations	There is a need to expand the structure to perform cytology in a large scale in KSA
Monitoring and evaluation	
Research priorities	There is need to have an accurate register of local data regarding the incidence and outcomes of CIN2+

Evidence profile: 3.1 Diagnostic test accuracy (DTA) evidence profile: VIA followed by colposcopy compared to cytology (ASCUS) followed by colposcopy
Author(s):RBP, JB, NS, RM
Date: 2013-11-28

Outcome	No. of studies (No. of patients)*	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		VIA followed by colposcopy**	Cytology followed by colposcopy**	
True positives (patients with CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies[11111111]	Serious[1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	15	16-17	CRITICAL
TP absolute difference									1-2 less		
True negatives (patients without CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	878-980	912-980	CRITICAL
TN absolute difference									0-34 less		
False positives (patients incorrectly classified as having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	0-102	0-68	CRITICAL
FP absolute difference									0-34 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[1]	None[4]	Serious[2]	None[3]	Undetected	⊕⊕⊖⊖ low	5	3-4	CRITICAL
FN absolute difference									1-2 more		

Diagnostic test accuracy

Pooled sensitivity VIA	77% (95% CI: 65 to 85)	Pooled sensitivity cytology **(AS-CUS)**	84% (95% CI: 76 to 90)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity VIA	82% (95% CI: 67 to 91)	Pooled specificity cytology **(AS-CUS)**	88% (95% CI: 79 to 93)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference Standard: Colposcopy with biopsy when indicated)

Footnotes:

***** This is the number of studies that assessed data for HPV test and cytology.

** The range represents the effect when the colposcopy is followed by impression or biopsy

[1] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. Downgraded one level in context of other factors, in particular indirectness.

[2] Estimates of HPV test, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. Downgraded one level in context of other factors, in particular imprecision.

[3] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

[4] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by colposcopy compared to cytology (ASCUS) followed by colposcopy

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)*						
	VIA →colp +/– CKC	VIA →colp +/– LEEP	VIA→colp +/– cryo	Cyto→colp +/– CKC	Cyto→colp +/–LEEP	Cyto→colp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	64-73	72-81	72-81	47-57	56-66	56-66	250
Cervical cancer incidence[2]	89-102	101-113	101-113	65-80	78-92	78-92	350
CIN2+ recurrence[3]	3420-3920	3898-4373	3898-4373	2514-3058	3034-3553	3034-3553	13 400
Undetected CIN2+ (FN)	5000			3000-4000			
Major bleeding[4]	132-1004	35-251	5-40	144-723	38-190	6-29	0
Premature delivery[5]	520-641	507-547	510-573	520-601	507-536	511-553	500
Infertility[6]	-	-	-	-	-	-	-
Major infections[7]	14-104	20-142	2-16	15-75	22-108	3-12	0
Minor infections[8]	144-1096	93-670	100-757	157-788	101-507	109-545	0
Unnecessarily treated (FP)	0-102000			0-68000			-
Cancer found at first-time screening[9]	3168			4794			0

Footnotes:

The colours in the table: In each GRADE evidence table, colour-coding is used to highlight the 'desirability' of the effects for that outcome relative to other outcomes. The continuum runs from light green (desirable) through yellow and orange to red (least desirable).

The numbers in the table are based on

* CIN2+ pretest probability 2%
* VIA: pooled sensitivity 77% (95% CI: 66 to 85), pooled specificity 82% (95% CI: 67 to 91)
* Cytology (ASCUS): pooled sensitivity 84% (95% CI: 76 to 90), pooled specificity 88% (95% CI: 79 to 93)
* Colposcopic impression: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)

* The overall QoE for each of these outcomes is very low ⊕⊖⊖⊖. Our lack of confidence in these effect estimates stems mainly from very low-quality evidence for treatment effects and natural progression/history data.
The numbers of events are presented as ranges. The lower value was obtained when colposcopy followed by biopsy data was used, whereas the higher value was obtained when colposcopy followed by impression data was used

[1] We assume no mortality from cervical cancer in true negative (TN) and false positive (FP). To calculate the mortality from cervical cancer, we assumed 250 deaths per 350 women with cervical cancer. These numbers are based on Eastern Africa age-standardized rates of cervical cancer and mortality provided by WHO at http://globocan.iarc.fr/, accessed 30 October 2012).
[2] We assume no cervical cancer in TN or FP. To calculate cervical cancer incidence in women with persistent CIN2+, we assumed 350 cervical cancers per 14 000 women who have persistent CIN2+ (i.e. FN). This incidence is based on Eastern Africa age-standardized rate of cervical cancer of 350 cervical cancers per 1 000 000 women, of whom 2% have CIN2+ (20 000 women with CIN2+, and a subsequent 30% regression for a total of 14 000 with persistent CIN2+). These data are available from WHO at http://globocan.iarc.fr/, accessed 30 October 2012).
[3] We assume no CIN2+ in TN and FP. Our calculations in the model are based on 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.
[4] We assumed major bleed would be 0 in TN and FN as they were not treated. We assumed 0.000339 of the population treated with cryotherapy, 0.002257 with LEEP, and 0.001705 with CKC, based on pooled proportions in observational studies with no independent controls, will have major bleeding.
[5] We assumed 5% population risk of premature delivery in 1% women who become pregnant. Based on pooled meta-analysis of controlled observational studies, 0.001125 of the population treated with cryotherapy, 0.000925 with LEEP, and 0.001705 of the population treated with CKC will have premature delivery.
[6] We did not identify any data about the risk of infertility after treatment for CIN2+.
[7] We assumed major infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control 0.000135 of the population treated with cryotherapy 0.001279 with LEEP, and 0.000888 with CKC will have major infection.
[8] We assumed minor infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.006473 of the population treated with cryotherapy, 0.006027 with LEEP, and 0.009368 with CKC will have minor infection.
[9] Cancers detected at first-time screening calculated from Sankaranarayanan et al. (2005). Numbers for single screening tests were calculated as 'screen-detected' cancers in women who participated in the screening programme; and numbers for test with colposcopy were calculated as 'screen detected' plus 'clinically detected' cancers. For a sequence of tests (e.g. HPV test followed by VIA), the greater number of cancers detected between tests was used. No cancers would be found in the 'no screen' group. This is not the annual incidence of cervical cancer (which is shown in a row above). It represents the cumulative rate of cancer development before screening started (i.e. the prevalence of cancer at the time when screening is conducted).
[10] 'No screen' numbers were calculated using the same assumptions above for FN, with the exception of premature delivery which was baseline risk in the population.

References to studies included in meta-analysis of diagnostic test accuracy

1. Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic Oncology*, 2001, 83(2):439–444.
    a. Pan Q et al. A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma a cross-sectional, comparative study. *Acta Cytologica*, 2003, 47(1):45–50.
2. Cremer M et al. Adequacy of visual inspection with acetic acid in women of advancing age. *International Journal of Gynaecology & Obstetrics*, 2011, 113(1):68–71.
3. De Vuyst H et al. Comparison of Pap smear, visual inspection with acetic acid, human papillomavirus DNA-PCR testing and cervicography. *International Journal of Gynaecology & Obstetrics*, 2005, 89(2):120–126.
4. Elit L et al. Assessment of 2 cervical screening methods in Mongolia: cervical cytology and visual inspection with acetic acid. *Journal of Lower Genital Tract Disease*, 2006, 10(2):83–88.
5. Ghaemmaghami F et al. Visual inspection with acetic acid as a feasible screening test for cervical neoplasia in Iran. *International Journal of Gynecological Cancer*, 2004, 14(3):465–469.
6. Goel A et al. Visual inspection of the cervix with acetic acid for cervical intraepithelial lesions. *International Journal of Gynaecology & Obstetrics*, 2005, 88(1):25–30.
7. Hedge D et al. Diagnostic value of acetic acid comparing with conventional Pap smear in the detection of colposcopic biopsy-proved CIN. *Journal of Cancer Research & Therapeutics*, 2011, 7(4):454–458.
8. Qiao YL et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncology*, 2008, 9(10):929–936.
9. Sahasrabuddhe VV et al. Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India. *International Journal of Cancer*, 2012, 130(1):234–240.
10. Sankaranarayanan R et al. Test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screening in Kerala, India. *International Journal of Cancer*, 2003, 106(3):404–408.
11. Sodhani P et al. Test characteristics of various screening modalities for cervical cancer: a feasibility study to develop an alternative strategy for resource-limited settings. *Cytopathology*, 2006, 17(6):348–352.

References to studies included for diagnostic test accuracy of colposcopic impression

1. Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic Oncology*, 2001, 83(2):439–444.
2. Cantor SB et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. *Obstetrics & Gynecology*, 2008, 111(1):7–14.
3. Cremer ML et al. Digital assessment of the reproductive tract versus colposcopy for directing biopsies in women with abnormal Pap smears. *Journal of Lower Genital Tract Disease*, 2010, 14(1):5–10.
4. Cristoforoni PM et al. Computerized colposcopy: results of a pilot study and analysis of its clinical relevance. *Obstetrics & Gynecology*, 1995, 85(6):1011–1016.
5. Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. *Journal of the Turkish German Gynecology Association*, 2009, 10(4):205–207.
6. Ferris DG, Miller MD. Colposcopic accuracy in a residency training program: defining competency and proficiency. *Journal of Family Practice*, 1993, 36(5):515–520.

7. Homesley HD, Jobson VW, Reish RL. Use of colposcopically directed, four-quadrant cervical biopsy by the colposcopy trainee. *Journal of Reproductive Medicine*, 1984, 29(5):311–316.
8. Jones DE et al. Evaluation of the atypical Pap smear. *American Journal of Obstetrics & Gynecology*, 1987, 157(3):544–549.
9. Kierkegaard O et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetricia et Gynecologica Scandinavica*. 1994;73(8):648–651.
10. Mousavi AS et al. A prospective study to evaluate the correlation between Reid colposcopic index impression and biopsy histology. *Journal of Lower Genital Tract Disease*, 2007, 11(3):147–150.
11. Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: is VIA superseding Pap smear? *Journal of SAFOG*, 2011, 3 (3):131–134.

Evidence to recommendation framework 4

Should treatment with Cryotherapy be preferred over treatment with CKC to treat women who test positive after HPV test followed by colposcopy or cytology followed by colposcopy?

Population: Women at risk of cervical cancer
Options: Cryotherapy
Comparison: CKC
Setting: Community
Perspective: Public Health/ Policy making (Ministry of Health)

Background: This is an adaptation of the "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention". The objective of this adaptation is to make the recommendations applicable to the context of Saudi Arabia. The following difference/remark was detected with respect to the original guidelines question and of relevance to this recommendation question: The majority of women would undergo histological confirmation, and thus all screening strategies have to be followed by colposcopy

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is estimated that approximately 1–2% of women have CIN2+ each year. If left untreated, CIN2+ can progress to cervical cancer. In Saudi Arabia. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year (source: Globocan 2008). It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively.	Guideline panel thoughts: - Although cervical cancer used to be a rare condition, its incidence has increased over the last 10 years - There is an official national register (from 2005 to 2009, from which the globocan statistics collected information), but it may not be accurate since there may be underreporting issues. - Even though the incidence is not very high, mortality associated to cervical cancer is high, which makes this problem a priority

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	No included studies ☐ · Very low ☒ · Low ☐ · Moderate ☐ · High ☐
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ · Possibly important uncertainty or variability ☐ · Probably no important uncertainty or variability ☐ · No important uncertainty or variability ☒ · No known undesirable outcomes ☐
Are the desirable anticipated effects large?	No ☐ · Probably No ☒ · Uncertain ☐ · Probably Yes ☐ · Yes ☐ · Varies ☐
Are the undesirable anticipated effects small?	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ☒ · Varies ☐
Are the desirable effects large relative to undesirable effects?	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☒ · Yes ☐ · Varies ☐

RESEARCH EVIDENCE

Outcome	Relative importance	Certainty of the evidence
Mortality	CRITICAL	⊕⊕⊕⊖ moderate for the diagnostic accuracy of HPV and VIA
Cervical cancer incidence	CRITICAL	
CIN2+ recurrence	CRITICAL	
Undetected CIN2+	CRITICAL	
Major bleeding	CRITICAL	⊕⊖⊖⊖ very low for the effects of treatment and the natural progression of CIN
Premature delivery	IMPORTANT	
Infertility	IMPORTANT	
Major infections	CRITICAL	
Minor infections	IMPORTANT	
Unnecessary treatment	IMPORTANT	

Summary of findings: *See tables 1.2 and 2.2*

- *Cryotherapy results in less major bleedings, premature deliveries, major infections and minor infections than CKC*

ADDITIONAL CONSIDERATIONS

Evidence from qualitative studies suggests women may fear screening and may have a high level of anxiety related to colposcopy or treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. In addition, evidence from controlled trials showed that women find treatment by cryotherapy and LEEP acceptable, and are satisfied with a screen-and-treat approach. This evidence comes from developing countries. The panel of the original guideline considered that this information is applicable to most women in low and middle income countries

The guideline panel agreed that most women would prefer to undergo treatment with cryotherapy because it is a procedure that can be done as outpatient. The only disadvantage is an increase in secretions after treatment with cryotherapy, which may lead to need further control visits

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Although there is no official information, the guideline panel agreed that cryotherapy is much cheaper than CKC in KSA
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that cryotherapy would be a cost saving option
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / **Varies** ☐	No evidence found	The guideline panel agreed that health inequities would be reduced if cryotherapy is preferred over CKC
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that cryotherapy is an option acceptable to all key stakeholders. However, some concerns were raised due to negative past experiences where there was equipment failure and patient dissatisfaction after the procedure.
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that all treatment options are feasible to implement, including cryotherapy and CKC

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends to use cryotherapy over CKC to treat women at risk of cervical cancer who tested positive for CIN2+ (strong recommendation, very low quality evidence for health outcomes evidence)
Justification	Even though the quality of the evidence was very low for the evidence regarding the health outcomes, the panel agreed that the potential harms of CKC are very important (despite the lower confidence in the estimates of effects), and that patients' values and preferences had little variation. A high weight was given to these judgments, together with the potential reduction of health inequities, and no issues regarding acceptability and feasibility.
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	There is need for research regarding health outcomes after treatment with these options

Evidence to recommendation framework 5

Should treatment with LEEP be preferred over treatment with CKC to treat women who test positive for CIN2+ after HPV test followed by colposcopy or VIA followed by colposcopy?

Population: Women at risk of cervical cancer
Option: LEEP
Comparison: CKC
Setting: Community
Perspective: Public Health/ Policy making (Ministry of Health)

Background: This is an adaptation of the "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention". The objective of this adaptation is to make the recommendations applicable to the context of Saudi Arabia. The following difference/remark was detected with respect to the original guidelines question and of relevance to this recommendation question: The majority of women would undergo histological confirmation, and thus all screening strategies have to be followed by colposcopy

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is estimated that approximately 1–2% of women have CIN2+ each year. If left untreated, CIN2+ can progress to cervical cancer. In Saudi Arabia. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year (source: Globocan 2008). It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively.	Guideline panel thoughts: - Although cervical cancer used to be a rare condition, its incidence has increased over the last 10 years - There is an official national register (from 2005 to 2009, from which the globocan statistics collected information), but it may not be accurate since there may be underreporting issues. - Even though the incidence is not very high, mortality associated to cervical cancer is high, which makes this problem a priority

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☒ | *Low* ☐ | *Moderate* ☐ | *High* ☐
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☒ | *No known undesirable outcomes* ☐
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | *Varies* ☐
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | *Varies* ☐
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | *Varies* ☐

RESEARCH EVIDENCE

Outcome	Relative importance	Certainty of the evidence
Mortality	CRITICAL	⊕⊕⊕⊖ moderate for the diagnostic accuracy of HPV and VIA
Cervical cancer incidence	CRITICAL	
CIN2+ recurrence	CRITICAL	
Undetected CIN2+	CRITICAL	
Major bleeding	CRITICAL	⊕⊖⊖⊖ very low for the effects of treatment and the natural progression of CIN
Premature delivery	IMPORTANT	
Infertility	IMPORTANT	
Major infections	CRITICAL	
Minor infections	IMPORTANT	
Unnecessary treatment	IMPORTANT	

Summary of findings: *See tables 1.2 and 2.2*

- *LEEP results in more major infections than CKC*
- *LEEP results in less major bleedings, premature deliveries and minor infections than CKC*

ADDITIONAL CONSIDERATIONS

The panel revised and agreed on the outcomes ranking and judgments.

Evidence from qualitative studies suggests women may fear screening and may have a high level of anxiety related to colposcopy or treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. In addition, evidence from controlled trials showed that women find treatment by cryotherapy and LEEP acceptable, and are satisfied with a screen-and-treat approach. This evidence comes from developing countries. The panel of the original guideline considered that this information is applicable to most women in low and middle income countries

The guideline panel agreed that most women would prefer to receive treatment with LEEP over CKC due to the lower rate of complications and the possibility of performing the procedure in an outpatient clinic.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Although there is no official information, the guideline panel agrees that LEEP is cheaper than CKC
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that LEEP would be cost saving option
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / **Varies** ☐	No evidence found	The guideline panel agreed that health inequities would be reduced if LEEP is preferred over CKC
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that LEEP is an alternative acceptable to all key stakeholders
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that all treatment options are feasible to implement, including LEEP and CKC

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends to use LEEP over CKC to treat women at risk of cervical cancer who tested positive for CIN2+ (strong recommendation, very low quality evidence for health outcomes evidence)
Justification	Even though the quality of the evidence was very low for the evidence regarding the health outcomes, the panel agreed CKC can potentially cause large and relevant harms (despite the lower confidence in the estimates of effects), and that patients' values and preferences had little variation. A high weight was given to these judgments, together with the potential reduction of health inequities, and no issues regarding acceptability and feasibility.
Subgroup considerations	
Implementation considerations	In some centers, training may be required to implement LEEP
Monitoring and evaluation	
Research priorities	There is need for research regarding health outcomes after treatment with these options

Evidence to recommendation framework 6

Should treatment with Cryotherapy be preferred over treatment with LEEP to treat women who test positive for CIN2+ after HPV test followed by colposcopy or VIA followed by colposcopy?

Population: Women at risk of cervical cancer
Option: Cryotherapy
Comparison: LEEP
Setting: Community
Perspective: Public Health/ Policy making (Ministry of Health)

Background: This is an adaptation of the "WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention". The objective of this adaptation is to make the recommendations applicable to the context of Saudi Arabia. The following difference/remark was detected with respect to the original guidelines question and of relevance to this recommendation question: The majority of women would undergo histological confirmation, and thus all screening strategies have to be followed by colposcopy

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	It is estimated that approximately 1–2% of women have CIN2+ each year. If left untreated, CIN2+ can progress to cervical cancer. In Saudi Arabia. According to the Saudi registry 2007 report, cervical cancer is the 13th most frequent cancer in Saudi women and the 6th most frequent cancer in Saudi women between 15 and 44 years of age. The incidence rate in Saudi Arabia is one of the lowest in the world at 1.9 cases per 100,000 women, accounting for 2.6% of diagnosed cancer cases in women. The number of new cervical cancer cases is 152 cases per year, and the mortality is 55 cases per year (source: Globocan 2008). It is anticipated that as the population ages, there will be a dramatic increase in the incidence of cervical cancer. The estimated number of new cervical cancer cases and deaths in 2025 are 309 and 117, respectively.	Guideline panel thoughts: - Although cervical cancer used to be a rare condition, its incidence has increased over the last 10 years - There is an official national register (from 2005 to 2009, from which the globocan statistics collected information), but it may not be accurate since there may be underreporting issues. - Even though the incidence is not very high, mortality associated to cervical cancer is high, which makes this problem a priority

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☒ | Low ☐ | Moderate ☐ | High ☐		
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☐ | No important uncertainty or variability ☒ | No known undesirable outcomes ☐		
Are the desirable anticipated effects large?	No ☒ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐		
Are the undesirable anticipated effects small?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐		
Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | Varies ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	CRITICAL	⊕⊕⊕⊖ moderate for the diagnostic accuracy of HPV and VIA ⊕⊖⊖⊖ very low for the effects of treatment and the natural progression of CIN
Cervical cancer incidence	CRITICAL	
CIN2+ recurrence	CRITICAL	
Undetected CIN2+	CRITICAL	
Major bleeding	CRITICAL	
Premature delivery	IMPORTANT	
Infertility	IMPORTANT	
Major infections	CRITICAL	
Minor infections	IMPORTANT	
Unnecessary treatment	IMPORTANT	

Summary of findings: *See tables 1.2 and 2.2*

- Cryotherapy results in less major bleedings, major infections and minor infections

Evidence from qualitative studies suggests women may fear screening and may have a high level of anxiety related to colposcopy or treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. In addition, evidence from controlled trials showed that women find treatment by cryotherapy and LEEP acceptable, and are satisfied with a screen-and-treat approach. This evidence comes from developing countries. The panel of the original guideline considered that this information is applicable to most women in low and middle income countries

The guideline panel agrees that most women would prefer to undergo treatment with cryotherapy over LEEP.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that cryotherapy would be cheaper than LEEP
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that there is not incremental cost if cryotherapy is preferred over LEEP
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / **Varies** ☐	No evidence found	The guideline panel agreed that cryotherapy would probably reduce inequities, because its availability is better
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agreed that since cryotherapy is cheaper and easier to perform, it would be acceptable to all key stakeholders. However, some concerns were raised due to negative past experiences where there was equipment failure and patient dissatisfaction after the procedure.
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The guideline panel agrees that cryotherapy would be easier to implement than LEEP. In addition, the learning curve is less steep than that of LEEP in case training is needed.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel suggests to use cryotherapy over LEEP to treat women at risk of cervical cancer who tested positive for CIN2+ (conditional recommendation, very low quality evidence for health outcomes evidence)
Justification	The quality of the evidence was very low for the evidence regarding the health outcomes, and the balance between benefits and harms probably favours cryotherapy (despite the lower confidence in the estimates of effects). According to the guideline panel, patients' values and preferences had little variation. These judgments were weighted similarly to the potential reduction of health inequities, and no issues regarding acceptability and feasibility.
Subgroup considerations	
Implementation considerations	LEEP is a valid alternative particularly in settings where there are experienced physicians and the equipment is available
Monitoring and evaluation	
Research priorities	There is need for research regarding health outcomes after treatment with these options

Appendix 2: Search Strategies and Results

Screening

Database: **Embase**	
Search strategy:	**Date of search: 10/2013**
1 sensitiv*.tw. 2 "sensitivity and specificity" 3 diagnostic odds ratio*.tw. 4 likelihood ratio*.tw. 5 (receiver operator characteristic or receiver operating characteristic or receiver operator characteristics or receiver operating characteristics or roc or roc curve).tw. 6 cancer screening/ 7 diagnostic accuracy/ 8 diagnostic.tw. 9 di.fs. 10 predictive value*.tw. 11 or/1-10 12 exp uterine cervix disease/di 13 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. 14 (cin or cin1 or cin2* or cin3*).tw. 15 12 or 13 or 14 16 acetic acid/ or acetic acid.tw. 17 (via and visual).tw. 18 (visual adj inspection).tw. 19 AAT.tw. 20 or/16-19 21 (HPV adj5 (test* or detect*)).tw. 22 (papilloma virus adj5 (test* or detect*)).tw. 23 (papillomavirus adj5 (test* or detect*)).tw. 24 exp papilloma virus/ and (test* or detect*).tw. 25 or/21-24 26 vaginal smears/ 27 (pap* adj (smear* or test*)).tw. 28 cytolog*.tw. 29 or/26-28 30 20 and 25 31 20 and 29 32 25 and 29 33 25 or 30 or 31 or 32 34 33 and 11 and 15 Date limit: 1980- 10/2013 Study Types: Screening and diagnostic test accuracy studies	
Records Retrieved	5239

Database: **Ovid MEDLINE**	
Search strategy:	**Date of search: 10/2013**
1 cervical intraepithelial neoplasia/ 2 uterine cervical dysplasia/ 3 uterine cervical neoplasms/ 4 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. 5 (cin or cin2* or cin3* or cin1).tw. 6 1 or 2 or 3 or 4 or 5 7 Acetic Acid/ or acetic acid.tw. 8 (VIA and visual).tw. 9 (visual adj inspection).tw. 10 AAT.tw. 11 or/7-10 12 HPV.tw. 13 (papillomavirus or (papilloma adj virus)).tw. 14 exp papillomaviridae/ 15 (or/12-14) and (test* or detect*).tw. 16 Vaginal smears/ 17 (pap* adj (smear* or test*)).tw. 18 cytolog*.tw. 19 or/16-18 20 11 and 15 21 11 and 19 22 15 and 19 23 15 or 20 or 21 or 22 24 6 and 23 25 sensitiv:.mp. 26 predictive value:.mp. 27 accurac:.tw. 28 screen:.tw. 29 mass screening/ 30 diagnostic odds ratio*.tw. 31 likelihood ratio*.tw. 32 (receiver operator characteristic or receiver operating characteristic or receiver operator characteristics or receiver operating characteristics or roc or roc curve).tw. 33 (positiv* adj3 result*).tw. 34 or/25-33 35 24 and 34 Date limit: 1946 – 10/2013 Study Types: Screening and diagnostic test accuracy studies	
Records Retrieved	3793

Treatment

Database: **Embase**	
Search strategy:	**Date of search: 10/2013**
1 exp uterine cervix disease/ 2 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. 3 (cin or cin1 or cin2* or cin3*).tw. 4 1 or 2 or 3 (87283) 5 (co or dm or pc or si or su or th).fs. 6 4 and 5 7 (cone or coni?ation).tw. 8 (biopsy or knife or cold).tw. 9 7 and 8 10 cold knife.tw. 11 conization/ 12 9 or 10 or 11 13 (leep or lletz).tw. 14 electrosurgery.sh. 15 loop.tw. 16 or/13-15 17 cryotherapy.tw. 18 cryosurgery/ 19 17 or 18 20 (12 or 16 or 19) and 6 Date limit: 1980 – 10/2013 Study Types: Treatment (Randomized controlled trials and observational studies)	
Records Retrieved	2307

Database: **Ovid MEDLINE**	
Search strategy:	**Date of search: 10/2013**
1 cervical intraepithelial neoplasia/ 2 uterine cervical dysplasia/ 3 uterine cervical neoplasms/ 4 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. 5 (cin or cin2* or cin3* or cin1).tw. 6 1 or 2 or 3 or 4 or 5 7 (co or ae or su or th).fs. 8 6 and 7 9 (cone or coni?ation).tw. 10 (biopsy or knife or cold).tw. 11 9 and 10 12 cold knife.tw. 13 conization/ 14 11 or 12 or 13 15 14 and 8 16 (leep or lletz).tw. 17 electrosurgery.sh. 18 loop.tw. 19 or/16-18 20 19 and 8 21 cryotherapy.tw. 22 cryosurgery/ 23 21 or 22 24 23 and 8 25 15 or 20 or 24 Date limit: 1946- 10/2013 Study Types: Treatment (Randomized controlled trials and observational studies)	
Records Retrieved	1890

Database: **Ovid MEDLINE In-Process & Other Non-Indexed Citations**	
Search strategy:	**Date of search: 10/2013**
1 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. 2 (cin or cin2* or cin3* or cin1).tw. 3 1 or 2 4 cone biopsy.tw. 5 knife.tw. 6 cone.tw. 7 ckc.tw. 8 coni?ation.tw. 9 or/4-8 10 (leep or lletz).tw. 11 loop.tw. 12 10 or 11 13 cryotherapy.tw. 14 3 and (9 or 12 or 13) Study Types: Treatment (Randomized controlled trials and observational studies)	
Records Retrieved	126

Values and Preferences

Database: **Embase**	
Search strategy:	**Date of search: 11/2013**
1. patient$ participation.mp. or exp patient participation/ 2. patient$ satisfaction.mp. or exp patient satisfaction/ 3. attitude to health.mp. or exp Attitude to health/ 4. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$).mp. 5. (patient$ utilit$ or health utilit$).mp. 6. health related quality of life.mp. or exp "quality of life"/ 7. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/ 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. exp uterine cervix disease/ 10. exp uterine cervix carcinoma/ 11. ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. 12. uterus cancer/ 13. 9 or 10 or 11 or 12 14. Saudi Arab$.mp,in. or Saudi Arabia/ 15. Riyadh.mp,in. 16. Jeddah.mp,in. 17. Kh*bar.mp,in. 18. Dammam.mp,in. 19. 14 or 15 or 16 or 17 or 18 20. Kuwait$.mp,in. or Kuwait/ 21. United Arab Emirates.mp,in. or United Arab Emirates/ 22. Qatar$.mp,in. or Qatar/	

23. Oman$.mp,in. or Oman/
24. Yemen$.mp,in. or Yemen/
25. Bahr*in$.mp,in. or Bahrain/
26. 20 or 21 or 22 or 23 or 24 or 25
27. Middle East$.mp,in. or Middle East/
28. Jordan$.mp,in. or Jordan/
29. Libya$.mp,in. or Libya/
30. Egypt$.mp,in. or Egypt/
31. Syria$.mp,in. or Syria/
32. Iraq$/ or Iraq.mp,in.
33. Morocc$.mp,in. or Morocco/
34. Tunisia$.mp,in. or Tunisia/
35. Leban$.mp,in. or Lebanon/
36. West Bank.mp,in.
37. Iran$.mp,in. or Iran/
38. Turkey/ or (Turkey or Turkish).mp,in.
39. Algeria$.mp,in. or Algeria/
40. Arab$.mp,in. or Arabs/
41. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
42. 40 or 41
43. 19 or 26 or 42
44. 8 and 13 and 43

Date limit: 1974- 11/2013

Records Retrieved	124

Database: **Ovid MEDLINE & Ovid MEDLINE In-Process & Other Non-Indexed Citations**

Search strategy:	**Date of search: 11/2013**

1. patient$ participation.mp. or exp patient participation/
2. patient$ satisfaction.mp. or exp patient satisfaction/
3. attitude to health.mp. or exp Attitude to health/
4. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$).mp.
5. (patient$ utilit$ or health utilit$).mp.
6. health related quality of life.mp. or exp "quality of life"/
7. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. cervical intraepithelial neoplasia/
10. uterine cervical dysplasia/
11. uterine cervical neoplasms/
12. ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw.
13. (cin or cin2* or cin3* or cin1).tw.
14. 9 or 10 or 11 or 12 or 13
15. Saudi Arab$.mp,in. or Saudi Arabia/
16. Riyadh.mp,in.
17. Jeddah.mp,in.
18. Kh*bar.mp,in.
19. Dammam.mp,in.
20. 15 or 16 or 17 or 18 or 19
21. Kuwait$.mp,in. or Kuwait/
22. United Arab Emirates.mp,in. or United Arab Emirates/

23. Qatar$.mp,in. or Qatar/
24. Oman$.mp,in. or Oman/
25. Yemen$.mp,in. or Yemen/
26. Bahr*in$.mp,in. or Bahrain/
27. 21 or 22 or 23 or 24 or 25 or 26
28. Middle East$.mp,in. or Middle East/
29. Jordan$.mp,in. or Jordan/
30. Libya$.mp,in. or Libya/
31. Egypt$.mp,in. or Egypt/
32. Syria$.mp,in. or Syria/
33. Iraq$/ or Iraq.mp,in.
34. Morocc$.mp,in. or Morocco/
35. Tunisia$.mp,in. or Tunisia/
36. Leban$.mp,in. or Lebanon/
37. West Bank.mp,in.
38. Iran$.mp,in. or Iran/
39. Turkey/ or (Turkey or Turkish).mp,in.
40. Algeria$.mp,in. or Algeria/
41. Arab$.mp,in. or Arabs/
42. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
43. 41 or 42
44. 20 or 27 or 43
45. 8 and 14
46. 45 and 44

Date limit: 1946- 11/2013

Records Retrieved	108

Database: **PsychInfo**

Search strategy:	**Date of search: 11/2013**

1. client$ participation.mp. or exp client participation/
2. client$ satisfaction.mp. or exp client satisfaction/
3. exp Health Attitudes/
4. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$ or patient$ attitude$).mp.
5. (patient$ utilit$ or health utilit$).mp.
6. health related quality of life.mp. or exp "quality of life"/
7. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp.
8. (standard gambl$ or time trade off or willingness to pay or visual analog scale or (VAS or "visual analog$ adj 2 scal$")).mp.
9. exp Uterus/ or uteris.mp.
10. cervix.mp. or exp Cervix/
11. (cervi* or uter*).tw.
12. ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw.
13. 9 or 10 or 11
14. 12 and 13
15. Saudi Arab$.mp,in. or Saudi Arabia/
16. Riyadh.mp,in.
17. Jeddah.mp,in.
18. Kh*bar.mp,in.
19. Dammam.mp,in.

20. 15 or 16 or 17 or 18 or 19 21. Kuwait$.mp,in. or Kuwait/ 22. United Arab Emirates.mp,in. or United Arab Emirates/ 23. Qatar$.mp,in. or Qatar/ 24. Oman$.mp,in. or Oman/ 25. Yemen$.mp,in. or Yemen/ 26. Bahr*in$.mp,in. or Bahrain/ 27. 21 or 22 or 23 or 24 or 25 or 26 28. Middle East$.mp,in. or Middle East/ 29. Jordan$.mp,in. or Jordan/ 30. Libya$.mp,in. or Libya/ 31. Egypt$.mp,in. or Egypt/ 32. Syria$.mp,in. or Syria/ 33. Iraq$/ or Iraq.mp,in. 34. Morocc$.mp,in. or Morocco/ 35. Tunisia$.mp,in. or Tunisia/ 36. Leban$.mp,in. or Lebanon/ 37. West Bank.mp,in. 38. Iran$.mp,in. or Iran/ 39. Turkey/ or (Turkey or Turkish).mp,in. 40. Algeria$.mp,in. or Algeria/ 41. Arab$.mp,in. or Arabs/ 42. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 43. 41 or 42 44. 20 or 27 or 43 45. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 46. 45 and 14 and 44 Date limit: 1987- 11/2013	
Records Retrieved	7

Summary of Searches

Total No. Retrieved:	**239**
Embase:	124
Medline:	108
PsychInfo:	7
Duplicates: 70	
No. Total without duplicates**:**	**169**
Screening (Title and Abstract Review)	
No. Excluded: 162	
Included for Full Text review:	**7**
Selection (Full Text Review)	
No. Excluded: 4	
Reasons for exclu-sions:	
1. Related to healthcare practitioners' knowledge and attitudes (1) 2. Related to HPV vaccination (1) 3. Not related to screening tests and treatments considered (2)	

Cost Effectiveness

Database: **Embase**	
Search strategy:	**Date of search: 11/2013**

1. economic evaluation$.mp. or exp economic evaluation/
2. fee$.mp. or exp fee/
3. health care cost$.mp. or exp "health care cost"/
4. hospital cost$.mp. or exp "hospital cost"/
5. pharmacoeconomics.mp. or exp pharmacoeconomics/
6. health economics.mp. or health economics/
7. budget$.mp. or budget/
8. socioeconomics.mp. or socioeconomics/
9. 1 or 2 or 3 or 4 or 5 or 6
10. 7 or 9
11. 8 or 10
12. (low adj cost).mp.
13. (high adj cost).mp.
14. (health?care adj cost$).mp.
15. (cost adj estimate$).mp.
16. (cost adj variable$).mp.
17. (unit adj cost$).mp.
18. (fiscal or funding or financial or finance).tw.
19. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 11 or 20
22. exp uterine cervix disease/
23. exp uterine cervix carcinoma/
24. uterus cancer/
25. ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw.
26. (cin or cin1 or cin2* or cin3*).tw.
27. 22 or 23 or 24 or 25 or 26
28. (cone or coni?ation).tw.
29. (biopsy or knife or cold).tw.
30. 28 and 29
31. cold knife.tw.
32. conization/
33. 30 or 31 or 32
34. (leep or lletz).tw.
35. electrosurgery.sh.
36. loop.tw.
37. 34 or 35 or 36
38. cryotherapy.tw.
39. cryosurgery/
40. 38 or 39
41. acetic acid/ or acetic acid.tw.
42. (via and visual).tw.
43. (visual adj inspection).tw.
44. 41 or 42 or 43
45. (HPV adj5 (test* or detect*)).tw.
46. (papilloma virus adj5 (test* or detect*)).tw.
47. (papillomavirus adj5 (test* or detect*)).tw.
48. exp papilloma virus/ and (test* or detect*).tw.
49. 45 or 46 or 47 or 48
50. vagina smear/

51. (pap* adj (smear* or test*)).tw.
52. cytolog*.tw.
53. 50 or 51 or 52
54. Saudi Arab$.mp,in. or Saudi Arabia/
55. Riyadh.mp,in.
56. Jeddah.mp,in.
57. Kh*bar.mp,in.
58. Dammam.mp,in.
59. 54 or 55 or 56 or 57 or 58
60. Kuwait$.mp,in. or Kuwait/
61. United Arab Emirates.mp,in. or United Arab Emirates/
62. Qatar$.mp,in. or Qatar/
63. Oman$.mp,in. or Oman/
64. Yemen$.mp,in. or Yemen/
65. Bahr*in$.mp,in. or Bahrain/
66. 60 or 61 or 62 or 63 or 64 or 65
67. Middle East$.mp,in. or Middle East/
68. Jordan$.mp,in. or Jordan/
69. Libya$.mp,in. or Libya/
70. Egypt$.mp,in. or Egypt/
71. Syria$.mp,in. or Syria/
72. Iraq$/ or Iraq.mp,in.
73. Morocc$.mp,in. or Morocco/
74. Tunisia$.mp,in. or Tunisia/
75. Leban$.mp,in. or Lebanon/
76. West Bank.mp,in.
77. Iran$.mp,in. or Iran/
78. Turkey/ or (Turkey or Turkish).mp,in.
79. Algeria$.mp,in. or Algeria/
80. Arab$.mp,in. or Arabs/
81. 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
82. 80 or 81
83. 59 or 66 or 82
84. 33 or 37 or 40
85. 44 or 49 or 53
86. 84 or 85
87. 21 and 27 and 86 and 83

Date limit: 1974-11/2013

Records Retrieved	67

Data base: **Ovid MEDLINE & Ovid MEDLINE In-Process & Other Non-Indexed Citations**	
Search strategy:	**Date of search: 11/2013**

1. economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/
2. exp "Costs and Cost Analysis"/
3. Value-Based Purchasing/
4. exp "Fees and Charges"/
5. budget$.mp. or Budgets/
6. (low adj cost).mp.
7. (high adj cost).mp.
8. (health?care adj cost$).mp.
9. (cost adj estimate$).mp.
10. (cost adj variable$).mp.
11. (unit adj cost$).mp.
12. (fiscal or funding or financial or finance).tw.
13. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. cervical intraepithelial neoplasia/
16. uterine cervical dysplasia/
17. uterine cervical neoplasms/
18. ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw.
19. (cin or cin2* or cin3* or cin1).tw.
20. 15 or 16 or 17 or 18 or 19
21. (cone or coni?ation).tw.
22. (biopsy or knife or cold).tw.
23. 21 and 22
24. cold knife.tw.
25. conization/
26. 23 or 24 or 25
27. (leep or lletz).tw.
28. electrosurgery.sh.
29. loop.tw.
30. 27 or 28 or 29
31. cryotherapy.tw.
32. cryosurgery/
33. 31 and 32
34. Saudi Arab$.mp,in. or Saudi Arabia/
35. Riyadh.mp,in.
36. Jeddah.mp,in.
37. Kh*bar.mp,in.
38. Dammam.mp,in.
39. 34 or 35 or 36 or 37 or 38
40. Kuwait$.mp,in. or Kuwait/
41. United Arab Emirates.mp,in. or United Arab Emirates/
42. Qatar$.mp,in. or Qatar/
43. Oman$.mp,in. or Oman/
44. Yemen$.mp,in. or Yemen/
45. Bahr*in$.mp,in. or Bahrain/
46. 40 or 41 or 42 or 43 or 44 or 45

47. Middle East$.mp,in. or Middle East/
48. Jordan$.mp,in. or Jordan/
49. Libya$.mp,in. or Libya/
50. Egypt$.mp,in. or Egypt/
51. Syria$.mp,in. or Syria/
52. Iraq$/ or Iraq.mp,in.
53. Morocc$.mp,in. or Morocco/
54. Tunisia$.mp,in. or Tunisia/
55. Leban$.mp,in. or Lebanon/
56. West Bank.mp,in.
57. Iran$.mp,in. or Iran/
58. Turkey/ or (Turkey or Turkish).mp,in.
59. Algeria$.mp,in. or Algeria/
60. Arab$.mp,in. or Arabs/
61. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
62. 60 or 61
63. 39 or 46 or 62
64. Acetic Acid/ or acetic acid.tw.
65. (VIA and visual).tw.
66. (visual adj inspection).tw.
67. 64 or 65 or 66
68. HPV.tw.
69. (papillomavirus or (papilloma adj virus)).tw.
70. exp papillomaviridae/
71. 68 or 69 or 70
72. (test* or detect*).tw.
73. 71 and 72
74. Vaginal smears/
75. (pap* adj (smear* or test*)).tw.
76. cytolog*.tw.
77. 74 or 75 or 76
78. 33 or 26 or 30
79. 73 or 77 or 67
80. 78 or 79
81. 14 and 20 and 80 and 63

Date limit: 1946- 11/2013

Records Retrieved	17

Summary of Searches

Total No. Retrieved:	**84**
Embase:	67
Medline:	17
Duplicates: 19	
No. Total without duplicates**:**	**65**
Screening (Title and Abstract Review)	
No. Excluded:	**65**
Included for Full Text review:	**0**


المركز السعودي للرعاية الصحية المبنية على البراهين
The Saudi Center for Evidence Based Health Care
وزارة الصحة
Ministry of Health