Prevention of Cervical Cancer

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Prevention of Cervical Cancer

Guideline of the DGGG and the DKG (S3 Level, AWMF Register Number 015/027OL, December 2017) – Part 2 on Triage, Treatment and Follow-up

Prävention des Zervixkarzinoms

Leitlinie der DGGG und DKG (S3-Level, AWMF-Register-Nummer 015/027OL, Dezember 2017) – Teil 2 mit Abklärung, Therapie und Nachbetreuung

OPEN ACCESS

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Key words
cervical cancer, cervical intraepithelial neoplasia (CIN), cervical precancerous condition, HPV

Schlüsselwörter
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ABSTRACT

Aims Annual opportunistic screening for cervical carcinoma has been done in Germany since 1971. The creation of this S3 guideline meets an important need, outlined in the National Cancer Plan, with regard to screening for cervical cancer, as this guideline aims to provide important information and support for planned organized screening for cervical cancer in Germany.

Methods With the financial support of German Cancer Aid, 21 professional societies developed evidence-based statements and recommendations (classified using the GRADE system) for the screening, management and treatment of precancerous conditions of the cervix. Two independent scientific institutes compiled systematic reviews for this guideline.

Recommendations The second part of this short summary deals with the triage, treatment and follow-up care of cervical dysplasia. With regard to those women who do not participate in screening, the guideline authors recommend sending out repeat invitation letters or an HPV self-collection kit. Colposcopy should be carried out for further investigation if cytology findings are Pap II-p and HPV test results are positive or if the results of an HPV 16 or HPV 18 screening test are positive. A single abnormal Pap smear should be triaged and investigated using HPV testing or p16/Ki67 dual staining.

ZUSAMMENFASSUNG

Ziele Seit 1971 erfolgt in Deutschland die jährliche, opportunistische Früherkennungsuntersuchung des Zervixkarzinoms. Durch die Etablierung dieser S3-Leitlinie wird zum einen eine wichtige Forderung des Nationalen Krebsplans zum Zervixkarzinom-Screening erfüllt. Zum anderen kann die S3-Leitlinie wesentliche Informationen und Hilfestellungen für das geplante organisierte Zervixkarzinomscreening in Deutschland geben.

Methoden Mit finanzieller Unterstützung durch die Deutsche Krebshilfe wurden durch 21 Fachgesellschaften evidenzbasierte Statements und Empfehlungen (GRADE-System) zu Screening, Management und Behandlung von Zervixkarzinom-Vorstufen erarbeitet. Zwei unabhängige wissenschaftliche Institute haben systematische Reviews für diese Leitlinie erarbeitet.

Empfehlungen Der zweite Teil dieser Kurzzusammenfassung behandelt u. a. Abklärung, Therapie und Nachbetreuung zervikaler Dysplasien. Im Hinblick auf Nichtteilnehmerinnen am Screening empfiehlt die Leitliniengruppe erneute Einladungsschreiben oder eine HPV-Selbstabnahme. Ab einer Zytologie von Pap II-p in Kombination mit einem positiven HPV-Befund sollte eine Kolposkopie zur weiteren Abklärung durchgeführt werden, ebenso bei einem positiven HPV 16 oder HPV 18 Screening Test. Ein alleiniger auffälliger Pap-Abstrich sollte eine Triage mittels HPV-Test oder p16/Ki67 Dual-stain zur Folge haben.

I Guideline Information

The Oncology Guidelines Program of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., AWMF), the German Cancer Society (Deutsche Krebsgesellschaft e. V., DKG) and German Cancer Aid (Deutsche Krebshilfe, DKH).

Guidelines Program of the DGGG, the OEGGG and the SGGG.

For more information on the Guidelines Program, please refer to the end of this article.

Citation format

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Guideline documents

The complete long version with a list of the conflicts of interest of all authors and a short version are available in German on the homepage of the AWMF under:
https://www.awmf.org/leitlinien/detail/ll/015-027OL.html or
www.leitlinienprogramm-onkologie.de

Guideline authors

The German Society of Gynecology and Obstetrics (DGGG, mandate holder: Prof. Dr. Peter Hillemanns, Hanover) was the lead medical society responsible for the compilation of this guideline. The guideline is issued by the Oncological Guidelines Program. Every participating medical society nominated a mandate holder, with the board of the respective society confirming the mandate in writing. ▶ **Table 1** lists the medical societies and other organizations which participated in developing the guideline together with their respective mandated representatives. Only mandate holders nominated by participating societies and organizations were eligible to take part in the voting process (consensus process) after they had disclosed and excluded any conflicts of interest. A patient representative was directly involved in the compila-

▶ **Table 1** Participating professional societies and other organizations.

Participating professional societies and other organizations	Mandate holder
German Society of Gynecology and Obstetrics [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe], (DGGG)	Christian Dannecker
German Society for Epidemiology [Deutsche Gesellschaft für Epidemiologie], (DGEpi)	Stefanie Klug
German Society for Virology [Deutsche Gesellschaft für Virologie e. V.], (GfV)	Thomas Iftner
German Society of Pathology [Deutsche Gesellschaft für Pathologie e. V.], (DGP)	Thomas Löning Lars Horn (Deputy) Dietmar Schmidt (Deputy)
German STI Society [Deutsche STI-Gesellschaft e. V.], (DSTIG)	Hans Ikenberg
German Society for Cytology [Deutsche Gesellschaft für Zytologie], (DGZ)*	Heinrich Neumann (till 14.08.2013) Volker Schneider (till 12.05.2014)
German Society for Medical Informatics, Biometry and Epidemiology [Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e. V.], (GMDS)	Uwe Siebert Willi Sauerbrei (Deputy)
Gynecological Oncology Working Group of the DKG [Arbeitsgemeinschaft für gynäkologische Onkologie der DKG], (AGO)	Matthias Beckmann
Self-help for Women after Cancer [Frauenselbsthilfe nach Krebs e. V.]	Marion Gebhardt Heidemarie Haase (Deputy)
Professional Association of Gynecologists [Berufsverband der Frauenärzte e. V.], (BVF)*	Manfred Steiner Ulrich Freitag (Deputy)
Federal Association of Senior Physicians in Gynecology and Obstetrics [Arbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe e. V.], (BLFG)	Michael Friedrich
Professional Association of German Physicians Working in Cytology [Berufsverband zytologisch tätiger Ärzte in Deutschland e. V.], (AZÄD)*	Klaus Neis Bodo Jordan (Deputy)
Cervical Pathology and Colposcopy Working Group of the DGGG [Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der DGGG]*	Wolfgang Kühn Michael Menton (Deputy)
Prevention and Integrative Oncology Working Group of the DKG, Section B [Arbeitsgemeinschaft Prävention und integrative Onkologie (PRIO), DKG Sektion B]	Karsten Münstedt
HPV Management Forum of the Paul Ehrlich Society for Chemotherapy [HPV-Management-Forum (Paul-Ehrlich-Gesellschaft für Chemotherapie PEG e. V.)]	Achim Schneider Andreas Kaufmann (Deputy)
Colposcopy Study Group [Studiengruppe Kolposkopie e. V.]	K. Ulrich Petry
Working Group on Infections and Immunology of the DGGG [Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie der DGGG], (AGII)	Axel P. A. Schäfer
German Cancer Research Center, (DKFZ)	Magnus von Knebel-Doeberitz (till 25.06.2013) Michael Pawlita
International organizations	
Gynecological Oncology and Breast Health Working Group of the SGGG [Arbeitsgemeinschaft für gynäkologische Onkologie und Brustgesundheit (AGO) der SGGG]**	Mathias Fehr
Gynecological Oncology Working Group of the OEGGG [Arbeitsgemeinschaft für gynäkologische Onkologie (AGO) der OEGGG]**	Christoph Grimm Olaf Reich (Deputy)
European Society of Gynaecological Oncology, (ESGO)***	Rainer Kimmig Martin Heubner (Deputy)

* AG-CPC, AZÄD, BVF and DGZ stepped down from participating in the compilation of the guideline on 12 May 2014. After a number of constructive discussions by the ad-hoc committee, BVF re-joined the guideline authors on 4 September 2017.

** These international medical societies participated in the consensus process but had no voting rights.

*** Although the ESGO nominated a mandate holder and a deputy, they did not participate in the compilation of this guideline.

tion of this guideline. Ms. Marion Gebhardt (Frauenselbsthilfe nach Krebs e. V. [Self-help for Women after Cancer]) was involved in developing the guideline right from the start, attended the consensus conferences and had the right to vote in the consensus conferences.

II Guideline Application

Purpose and objectives

The creation of this S3 guideline meets an important need, outlined in the National Cancer Plan, with regard to screening for cervical cancer. The S3 guideline provides important information and support for the planned organized screening for cervical cancer in Germany.

The old German-language S2k guideline "Prevention, Diagnosis and Therapy of HPV Infections and Preinvasive Lesions of the Female Genitalia" was consulted, and the new guideline focused on those aspects which deal with the cervix. Guideline recommendations on primary prevention were taken from the updated German-language S3 guideline "082/002 Vaccination to Prevent HPV-associated Neoplasias" and supplemented with additional information about the impact of HPV vaccination on screening. The German-language S3 guideline "032/033OL Cervical Cancer: Diagnosis, Treatment and Follow-up" published in 2014 covers all aspects of invasive cervical cancer.

Targeted areas of patient care

This S3 guideline on the prevention of cervical cancer presents various aspects of the prevention of cervical cancer and the diagnosis, treatment and follow-up of cervical cancer including high-grade preinvasive lesions. The main priorities of the guideline were analyzing existing data in order to optimize screening strategies for cervical cancer by determining the optimal test procedures, organizations, investigative algorithms and treatments, and considering how best to encourage women who previously refused to attend screening to participate in the program. In addition, the guideline considered the impact of HPV vaccination on screening strategies for cervical cancer.

Target patient group

This S3 guideline is aimed at all women aged 20 and above.

Target user groups/target audience

The recommendations of the guideline are addressed to all physicians and professionals involved in screening for cervical cancer, particularly gynecologists, pathologists and cytologists as well as all healthcare professionals working in dysplasia outpatient clinics and centers.

Other target groups include:

- scientific medical societies and professional associations which are involved in screening for cervical cancer,
- women's advocacy groups (women's health organizations, patient and self-help organizations),
- quality assurance organizations and similar projects on national and federal state levels,
- healthcare policy institutions and decision-makers at national and federal state levels,
- payers,
- the general public to inform them about what constitutes good medical practice.

Adoption and period of validity

This guideline is valid from 31 December 2017 through to 31 December 2020. Because of the contents of the guideline, this period of validity is only an estimate. The guideline may need to be updated if new scientific evidence appears or the methodology used in the guideline is developed further. Moreover, the key statements and recommendations of the guideline should be subjected to regular editorial checks, and the contents of the guideline should be regularly reviewed.

III Methodology

Basic principles

The method used to prepare this guideline was determined by the class to which this guideline was assigned. The AWMF Guidance Manual (version 1.0) has set out the respective rules and requirements for different classes of guidelines. Guidelines are differentiated into lowest (S1), intermediate (S2) and highest (S3) class. The lowest class is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was divided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest S3 class combines both approaches. This guideline is classified as: S3.

Grading of evidence

The GRADE (GRADE = Grading of Recommendations Assessment, Development and Evaluation) system developed by the GRADE Working Group [1] (www.gradeworkinggroup.org) was used to evaluate the quality of evidence of the studies identified and used for this guideline (▶ **Table 2**).

▶ **Table 2** Grading of the quality of evidence based on the GRADE system.

GRADE	Beschreibung	Symbol
High quality	*"We are very confident that the true effect lies close to that of the estimate of the effect."*	⊕⊕⊕⊕
Moderate quality	*"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 quality	*"Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect."*	⊕⊕⊖⊖
Very low quality	*"We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect."*	⊕⊖⊖⊖

Grading of recommendations

The methodology of the Oncology Guidelines Program requires guideline authors to assign a level of recommendation to each recommendation which indicates the strength of the recommendation. The strength of each recommendation is agreed upon in a formal consensus process which requires structured consensus conferences [2]. (Details are available in the German-language Guideline Report.) As part of this process, the mandate holders with voting rights formally voted on the recommendations in this guideline.

This guideline includes information on the grading of the evidence of the underlying studies used for all evidence-based Statements and Recommendations and additionally shows the strength of each recommendation (level of recommendation). In accordance with the AWMF Guidance Manual [2], this guideline differentiates between three strengths or levels of recommendation, and the respective level of recommendation is reflected by the syntax used in the recommendation (▶ **Table 3**).

The decision criteria used to determine the level of recommendation are explained in the German-language Guideline Report for this guideline.

▶ **Table 3** Level of recommendation.

Level of recommendation	Description	Syntax
A	Strong recommendation	must
B	Recommendation	should
0	Open recommendation	may

Statements

Statements are expositions or explanations of specific facts, circumstances, or problems, with no direct recommendations for action. Statements are adopted after a formal consensus process using the same approach as that used when formulating recommendations and can be based either on study results or expert opinions (▶ **Table 4**).

▶ **Table 4** Level of consensus.

Level of consensus	Extent of agreement in percent
Strong consensus	> 95 % of participants entitled to vote agree
Consensus	> 75–95 % of participants entitled to vote agree
Majority agreement	> 50–75 % of participants entitled to vote agree
No consensus	< 50 % of participants entitled to vote agree

Expert consensus (EC)

Statements/Recommendations which were issued based on the expert consensus of the guideline authors are identified as being based on expert consensus. No symbols or letters are used to grade the level of expert consensus; the respective level of consensus is demonstrated by the syntax used (must/should/may) in accordance with the differentiation described in ▶ **Table 3**.

IV Guideline

1 Differential diagnosis and evaluation algorithm

No.	Recommendations/Statements	GRADE	Sources
10.1.	If a cytological finding is classified as group IIa, the treating gynecologist should be informed that abnormal findings were detected previously (in the last 2 years) and that the patient should continue to be monitored. Additional work-ups to obtain a differential diagnosis are only indicated if they are necessary in the current constellation to avoid overtreatment.	EC	

1.1 Indication for coloscopy depends on probability of CIN 3

No.	Recommendations/Statements	GRADE	Sources
10.2.	A colposcopic work-up should be done if the post-test probability for an average cumulative risk of CIN 3+ is 10 % or more.	EC	

1.2 What is the best diagnostic work-up strategy to investigate abnormal cytology

1.2.1 Atypical squamous or glandular cells (Pap II-p, II-g)

No.	Recommendations/Statements	GRADE	Sources
10.3.	If the findings obtained during organized cytological screening are classified as group II-p ~ ASC-US and II-g ~ AGUS, HR-HPV testing should be done after 6 months. If the HR-HPV test is positive, a colposcopic work-up should be done within 3 months. If the HPV test is negative, the patient should be followed up by HPV testing and cytology after 12 months.	⊕⊕⊕⊖ B	[3 – 53]
10.4.	If the findings obtained during organized cytological screening are classified as group II-p ~ ASC-US and II-g ~ AGUS, p16/Ki-67 testing may be carried out after 6 months. If the results of dual staining with p16/Ki-67 are positive, a colposcopic work-up should be performed within 3 months. If the results of dual staining with p16/Ki-67 are negative, the patient should be followed up with HPV testing and cytology after 12 months.	⊕⊖⊖⊖ 0	[43, 54 – 56]

1.2.2 Cytological suspicion of low-grade dysplasia (Pap IIID1)

No.	Recommendations/Statements	GRADE	Sources
10.5.	If the findings obtained during organized cytological screening are classified as group IIID1 ~ LSIL, a diagnostic work-up based on HR-HPV testing should be carried out after 6 months. If the HR-HPV test is positive, a colposcopic work-up should be done within 3 months. If the HPV test is negative, the patient should be followed up with HPV testing and cytology after 12 months.	⊕⊕⊕⊖ B	[4, 5, 8, 10, 13, 17, 23, 26 – 29, 31, 32, 35, 39, 41 – 43, 45 – 49, 51 – 53, 57 – 68]
10.6.	If the findings obtained during organized cytological screening are classified as group IIID1 ~ LSIL, a diagnostic work-up based on p16/Ki-67 testing should be done after 6 months. If the results of this dual staining with p16/Ki-67 are positive, the patient should be investigated further by colposcopy within 3 months. If the results of dual staining with p16/Ki-67 are negative, the patient should be followed up with HPV testing and cytology after 12 months.	⊕⊖⊖⊖ 0	[43, 55, 56, 68, 69]

1.2.3 Unclear cytological findings classified as Pap III-p, III-g, III-x

No.	Recommendations/Statements	GRADE	Sources
10.7.	a) If the findings obtained during organized cytological screening are classified as group III-p, III-x, III-e or III-g, a diagnostic work-up based on either HR-HPV testing or p16/Ki-67 immunocytochemistry may be carried out within 3 months. If the HR-HPV test or the results of dual staining with p16/Ki-67 are positive, a colposcopic work-up should be done within 3 months. If the diagnostic tests are negative, the patient should be followed up with HPV testing and cytology after 12 months. b) If the findings obtained during organized cytological screening are classified as group III-x, III-e and III-g, an endometrium-specific work-up should be done to exclude endometrial neoplasia (vaginal ultrasound, hysteroscopy, fractionated curettage, etc.).	EC	

1.2.4 Moderate and high-grade cytological abnormalities (Pap IIID2, Pap IVa, Pap IVb, Pap V)

No.	Recommendations/Statements	GRADE	Sources
10.8.	If the findings obtained during organized cytological screening are classified as group IIID2, IV a–p, IV a–g, IV b–p, IV b–g, V-p, V-g, V-e or V-x, diagnostic colposcopy must be carried out.	EC	

1.3 What are the best diagnostic work-up strategies for patients with a positive HPV test at screening and aged > 30 years?

No.	Recommendations/Statements	GRADE	Sources
10.9.	If the results of an HPV test done as part of routine screening are positive, a diagnostic work-up using cytology should be carried out.	⊕⊕⊖⊖ B	[70 – 79]
10.10.	If the results of an HPV test done as part of routine screening are positive, a diagnostic work-up using p16/Ki-67 testing may be carried out.	⊕⊖⊖⊖ 0	[72, 73]
10.11.	If the results of an HPV-16/18 test carried out as part of HPV-based screening are positive, a diagnostic work-up using colposcopy should be carried out.	⊕⊖⊖⊖ B	[77, 79]
10.12.	If the results of a routine screening HPV test are positive and the results of diagnostic cytology or the results of combined HPV and Pap screening are classified as group II-p or above, a diagnostic work-up using colposcopy should be carried out.	EC	

2 Colposcopy

2.1 Use of diagnostic colposcopy

No.	Recommendations/Statements	GRADE	Sources
11.1.	Colposcopy must not be used for screening.	EC	
11.2.	If there is a high suspicion of CIN 3+ or ACIS/adenocarcinoma (risk ≥ 10 %*), diagnostic colposcopy must be carried out ▪ to histologically confirm squamous and glandular atypia/neoplasia, ▪ to determine the surgical strategy.	EC	
11.3.	If the transformation zone is classified as Type 1 or Type 2 at diagnostic colposcopy, colposcopy-guided biopsies should be obtained from the highest-grade lesion(s); if the transformation zone is classified as Type 3, endocervical curettage should be carried out.	EC	

* Post-test probability

2.2 Quality criteria for diagnostic colposcopy or dysplasia clinics

No.	Recommendations/Statements	GRADE	Sources
11.4.	Diagnostic colposcopy procedures must be carried out by a dysplasia clinic or dysplasia unit certified in accordance with the requirements of the DKG/DGGG/AGO/AG-CPC/EFC.	EC	

3 Healthcare structures

No.	Recommendations/Statements	GRADE	Sources
12.1.	Around 50 % of women in Germany participate annually in cancer screening (*Krebsfrüherkennungsuntersuchung*, KFU) which has been recommended in Germany since 1971 and screens participants for cervical cancer. Around 70 % of women participate in screening at least once every 3 years.	EC	
12.2.	In Germany, rates of participation in cervical cancer screening (KFU) are lower for women with a low socio-economic status and/or for women of advanced age.	EC	
12.3.	Organized screening with population-based invitations to attend screening and more stringent quality controls may result in more effective and more balanced screening in terms of the socio-economic status and the age of participants.	EC	

4 Strategy for non-participation in screening

4.1 Letters of invitation

No.	Recommendations/Statements	GRADE	Sources
13.1.	The repeated sending of letters of invitation to attend screening as part of an organized screening program results in an only marginal increase in participation rates among those women who have not previously participated in regular screening.	⊕⊕⊖⊖	[80 – 84]

4.2 HPV self-collection

No.	Recommendations/Statements	GRADE	Sources
13.2.	The participation rates of women who did not participate in cancer screening despite receiving a letter of invitation can be doubled with HPV self-collection.	⊕⊕⊕⊖ B	[85 – 94]
13.3.	Self-sampling should therefore be offered to these women (nonresponders).	⊕⊕⊕⊖ B	[85 – 94]
13.4.	HPV self-collection for screening must be reserved for those women who do not otherwise participate in cancer screening.	⊕⊕⊕⊖ A	[89, 95 – 127]

5 Treatment

5.1 Appropriate treatment methods for squamous and glandular cervical intraepithelial neoplasia

No.	Recommendations/Statements	GRADE	Sources
14.1.	Loop excision and laser excision are the methods of choice to treat squamous and glandular cervical intraepithelial neoplasia.	⊕⊖⊖⊖ A	[128 – 130]
14.2.	Cold-knife conization may be used as an alternative to treat glandular intraepithelial neoplasia.	⊕⊖⊖⊖ 0	[128]
14.3.	After histological confirmation using punch biopsy, laser vaporization must only be used to treat CIN 1, CIN 2 or CIN 3 if all of the following conditions are met: ▪ the whole transformation zone can be visualized (T-Zone Type 1), ▪ there are no indications of any changes in the glandular epithelium, ▪ there are no indications of any invasive process, ▪ there are no discrepancies between cytological, colposcopic and histological assessments of the biology of any changes, ▪ the patient is not older than 50 years.	EC	

5.2 Treatment under colposcopic control

No.	Recommendations/Statements	GRADE	Sources
14.4.	Treatment, whether it consists of excision or ablative procedures, must be carried out under colposcopic control.	EC	

5.3 Management of CIN

5.3.1 Monitoring, testing or treatment for CIN 1

No.	Recommendations/Statements	GRADE	Sources
14.5.	If CIN 1 is confirmed histologically, the initial approach must be to wait and see and re-evaluate the patient after 6 months*.	EC	
14.6.	If CIN 1 is accompanied by Pap smear results classified as group IVa or higher and the lesion cannot be adequately evaluated and extends into the endocervix, the endocervical canal must be evaluated by histopathology.	EC	

* Colposcopy with a positive predictive value for CIN 2 or CIN 3 of at least 65 % is recommended if the patient is managed with expectant monitoring or undergoes purely ablative treatment [130].

5.3.2 Monitoring or treatment for CIN 2

No.	Recommendations/Statements	GRADE	Sources
14.7.	If a histologically confirmed CIN 2 lesion can be evaluated in its entirety and the transitional area between squamous and columnar epithelium can be entirely visualized, the initial approach is to wait and see and re-examine the patient after 6 months*.	EC	
14.8.	If the transitional area between squamous and columnar epithelium cannot be entirely visualized in a patient with a histologically confirmed CIN 2 lesion and/or at least one Pap smear was classified as IVa, the endocervical canal must be evaluated by histopathology.	EC	

* Colposcopy with a positive predictive value for CIN 2 or CIN 3 of at least 65 % is recommended if the patient is managed with expectant monitoring or undergoes purely ablative treatment [130].

5.3.3 Treatment for CIN 3

No.	Recommendations/Statements	GRADE	Sources
14.9.	A lesion confirmed histopathologically as CIN 3 must be resected.	EC	

5.3.4 Treatment recommendations for adolescents

No.	Recommendations/Statements	GRADE	Sources
14.10.	A conservative strategy must be used for women up to the age of 24 with histopathologically confirmed CIN 2 and can be used for women up to the age of 24 with histopathologically confirmed CIN 3, provided ▪ the lesion can be evaluated colposcopically in its entirety, and ▪ it does not contain any atypical glandular components, and ▪ an invasive process can be excluded with a high degree of certainty. Treatment should be carried out if the CIN 2 persists for more than 24 months or the CIN 3 persists for more than 12 months or the lesion expands into the endocervix. Treatment must be tissue-sparing.*	EC	
14.11.	Women up to the age of 24 with CIN 3 who are managed conservatively should be monitored by a certified dysplasia clinic (s. Chapter 2 Colposcopy).	EC	

* Colposcopy with a positive predictive value for CIN 2 or CIN 3 of at least 65 % is recommended if the patient is managed with expectant monitoring or undergoes purely ablative treatment [130].

5.3.5 Excision procedures vs. hysterectomy for cervical adenocarcinoma in situ (ACIS)

No.	Recommendations/Statements	GRADE	Sources
14.12.	The definitive histopathological diagnosis of ACIS (with the differential diagnosis excluding invasive adenocarcinoma) must be obtained by excision. Hysterectomy should be the definitive treatment for ACIS if the patient plans to have no more children. If the patient wishes to have children, R0 resection must be carried out and the patient must be followed up using colposcopy, cytology and HPV testing.	EC	

5.3.6 R0 resection and approach for R1 resection

No.	Recommendations/Statements	GRADE	Sources
14.13.	The goal must be to achieve R0 resection of a CIN 3.	EC	
14.14.	If the resection status after surgical excision of a CIN 3 is R1 and there is no suspicion of invasive cancer, the patient must attend a follow-up appointment after 6 months with cytology and HPV testing. If the findings at follow-up show that CIN 3 has persisted, the patient must be re-operated.	EC	

6 Pregnancy

No.	Recommendations/Statements	GRADE	Sources
15.1.	The indications for colposcopy (and biopsy, if required) during pregnancy are the same as those for non-pregnant women.	EC	
15.2.	During pregnancy, the investigation of abnormal cervical cancer screening results should be done by a DKG/AG-CPC-certified dysplasia clinic.	EC	
15.3.	Endocervical curettage must not be performed during pregnancy. An endocervical smear extending deep into the endocervical canal should not be done during pregnancy.	EC	
15.4.	If the results of the investigation (obtained by cytology, colposcopy and histologically if necessary) exclude high-grade dysplasia and carcinoma, no further colposcopy and/or cytological investigations are required during pregnancy.	EC	

6.1 Approach for CIN 2/CIN 3 and ACIS in pregnancy

No.	Recommendations/Statements	GRADE	Sources
15.5.	Pregnant women with CIN 2/CIN 3 or ACIS must not be treated surgically if invasive cancer can be excluded with a high degree of certainty.	EC	
15.6.	Pregnant women with CIN 2/CIN 3 or ACIS must be monitored regularly by colposcopy. The pregnant patient must be evaluated by colposcopy every three months.	EC	
15.7.	Excision to obtain histological confirmation is indicated in pregnant women if it is not possible to exclude invasive carcinoma by cytology, colposcopy and biopsy with any high degree of certainty.	EC	

6.2 Birth procedure when CIN 2/3 is present

No.	Recommendations/Statements	GRADE	Sources
15.8.	The presence of CIN 2/CIN 3 must have no impact on the decision about the birth procedure.	EC	

6.3 Obstetric complications after treatment for CIN

No.	Recommendations/Statements	GRADE	Sources
15.9.	Excision procedures performed during pregnancy are associated with significant obstetric risks such as preterm birth. Previous excision procedures are also associated with higher risk in subsequent pregnancies.	EC	
15.10.	As cold-knife conization is associated with the highest obstetric risk, it must not be carried out in women who still wish to have children.	EC	

7 Follow-up care

7.1 Follow-up with HPV testing and cytology after treatment for CIN

No.	Recommendations/Statements	GRADE	Sources
16.1.	Follow-up after treatment for CIN/ACIS must consist of examinations combining HPV testing and cytology.	⊕⊕⊖⊖ A	[131 – 146]
16.2.	Differential colposcopy should be performed if the findings at follow-up are abnormal (at least 1 of the test results is positive).	⊕⊕⊖⊖ B	[131 – 146]

7.1.1 Time and duration of follow-up

No.	Recommendations/Statements	GRADE	Sources
16.3.	Follow-up examinations combining HPV testing and cytology should be performed at 6, 12 and 24 months after completing treatment. The patient must continue to participate in regular screening, even if the findings at follow-up are unremarkable.	EC	

7.2 Importance of biomarkers during follow-up after treatment for CIN

7.2.1 Resection margin as a predictor for recurrence of treated CIN

No.	Recommendations/Statements	GRADE	Sources
16.4.	Follow-up after treatment for CIN/ACIS must consist of examinations combining HPV testing and cytology.	⊕⊖⊖⊖	[134 – 136, 147 – 152]

7.2.2 Other biomarkers as predictors for recurrence of treated CIN 2/3 lesion

No.	Recommendations/Statements	GRADE	Sources
16.5.	Biomarkers (5-type HPV mRNA, HPV type-specific persistence) must not be used to follow up patients treated for CIN 2/3 lesions.	⊕⊖⊖⊖ A	[134, 137, 151, 153 – 157]

8 Complementary, alternative and integrative medicine

8.1 Alternative medical diagnostic methods

No.	Recommendations/Statements	GRADE	Sources
17.1.	Alternative medical diagnostic methods must not be used to detect cervical dysplasia or establish a predisposition for cervical dysplasia.	EC	

8.2 Alternative medical treatment

No.	Recommendations/Statements	GRADE	Sources
17.2.	Alternative medical treatments of dysplasia should be rejected.	EC	

8.3 Complementary medical treatment

No.	Recommendations/Statements	GRADE	Sources
17.3.	It is not possible to make any recommendations about complementary medical treatments because of the lack of meaningful studies.	EC	

9 Patient education and information, dealing with psychological stress

9.1 Patient education and information given to women participating in cervical cancer screening

No.	Recommendations/Statements	GRADE	Sources
18.1.	Information given to the women who participate in screening for cervical cancer must cover the following aspects: ▪ an explanation of the disease, ▪ the natural progression of infection with HPV and associated cell changes, ▪ the different HPV types, ▪ the risk factors for cervical cancer, ▪ the impact on the patient's partner(s), ▪ a description of the screening method, ▪ information about the benefits and harm of screening methods, ▪ information on the quality of the screening methods.	EC	

9.2 Educating patients about their diagnosis, treatment options and follow-up care

No.	Recommendations/Statements	GRADE	Sources
18.2.	The information given to women with findings at screening which require further investigation must include the following: ▪ the findings ▪ the differential diagnosis ▪ the treatment options ▪ the treatment goals ▪ the duration of the different treatments and how they are carried out ▪ the necessity of regular follow-up appointments	EC	

10 Cost-effectiveness

No.	Recommendations/Statements	GRADE	Sources
19.1.	HPV-based screening performed every 3 years has a relatively favorable cost-effectiveness ratio. Compared to annual cytology-based screening, HPV-based screening has a similar expected benefit and a lower expected harm (e.g. surgical interventions, colposcopies, psychological stress caused by abnormal findings and follow-up examinations).	⊕⊖⊖⊖	[cf. Guideline Report and Evidence Report]
19.2.	In Germany, HPV-based screening carried out at intervals of every 3–5 years is considered to be cost-effective. HPV-based screening carried out at intervals of every 2 years has a less favorable cost-effectiveness ratio. Annual screening significantly increases costs without generating a significant additional benefit.	⊕⊖⊖⊖	[158]

Conflict of Interest

See guideline report: https://www.awmf.org/uploads/tx_szleitlinien/015-027OLm_Praevention_Zervixkarzinom_2018-01.pdf

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Prävention des Zervixkarzinoms

Leitlinie der DGGG und DKG (S3-Level, AWMF-Register-Nummer 015/027OL, Dezember 2017) – Teil 2 mit Abklärung, Therapie und Nachbetreuung

Prevention of Cervical Cancer

Guideline of the DGGG and the DKG (S3 Level, AWMF Register Number 015/027OL, December 2017) – Part 2 on Triage, Treatment and Follow-up

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ZUSAMMENFASSUNG

Ziele Seit 1971 erfolgt in Deutschland die jährliche, opportunistische Früherkennungsuntersuchung des Zervixkarzinoms. Durch die Etablierung dieser S3-Leitlinie wird zum einen eine wichtige Forderung des Nationalen Krebsplans zum Zervixkarzinom-Screening erfüllt. Zum anderen kann die S3-Leitlinie wesentliche Informationen und Hilfestellungen für das geplante organisierte Zervixkarzinomscreening in Deutschland geben.

Methoden Mit finanzieller Unterstützung durch die Deutsche Krebshilfe wurden durch 21 Fachgesellschaften evidenzbasierte Statements und Empfehlungen (GRADE-System) zu Screening, Management und Behandlung von Zervixkarzinom-Vorstufen erarbeitet. Zwei unabhängige wissenschaftliche Institute haben systematische Reviews für diese Leitlinie erarbeitet.

Empfehlungen Der zweite Teil dieser Kurzzusammenfassung behandelt u. a. Abklärung, Therapie und Nachbetreuung zervikaler Dysplasien. Im Hinblick auf Nichtteilnehmerinnen am Screening empfiehlt die Leitliniengruppe erneute Einladungsschreiben oder eine HPV-Selbstabnahme. Ab einer Zytologie von Pap II-p in Kombination mit einem positiven HPV-Befund sollte eine Kolposkopie zur weiteren Abklärung durchgeführt werden, ebenso bei einem positiven HPV 16 oder HPV 18 Screening Test. Ein alleiniger auffälliger Pap-Abstrich sollte eine Triage mittels HPV-Test oder p16/Ki67 Dual-stain zur Folge haben.

ABSTRACT

Aims Annual opportunistic screening for cervical carcinoma has been done in Germany since 1971. The creation of this S3 guideline meets an important need, outlined in the National Cancer Plan, with regard to screening for cervical cancer, as this guideline aims to provide important information and support for planned organized screening for cervical cancer in Germany.

Methods With the financial support of German Cancer Aid, 21 professional societies developed evidence-based statements and recommendations (classified using the GRADE system) for the screening, management and treatment of precancerous conditions of the cervix. Two independent scientific institutes compiled systematic reviews for this guideline.

Recommendations The second part of this short summary deals with the triage, treatment and follow-up care of cervical dysplasia. With regard to those women who do not participate in screening, the guideline authors recommend sending out repeat invitation letters or an HPV self-collection kit. Colposcopy should be carried out for further investigation if cytology findings are Pap II-p and HPV test results are positive or if the results of an HPV 16 or HPV 18 screening test are positive. A single abnormal Pap smear should be triaged and investigated using HPV testing or p16/Ki67 dual staining.

I Leitlinieninformationen

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), Deutschen Krebsgesellschaft e. V. (DKG) und Deutschen Krebshilfe (DKH).

Leitlinienprogramm der DGGG, OEGGG und SGGG.

Informationen dazu am Ende des Artikels.

Zitationsformat

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Leitliniendokumente

Die vollständige Langversion mit einer Aufstellung der Interessenkonflikte aller Autoren und eine Kurzversion können auf der Homepage der AWMF eingesehen werden:
https://www.awmf.org/leitlinien/detail/ll/015-027OL.html oder
www.leitlinienprogramm-onkologie.de

Leitliniengruppe

Federführende Fachgesellschaft bei der Leitlinienerstellung ist die Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG, Mandatsträger Univ.-Prof. Dr. Peter Hillemanns, Hannover). Herausgeber der Leitlinie ist das Onkologische Leitlinienprogramm. Jede beteiligte Fachgesellschaft hat einen Mandatsträger benannt, der schriftlich vom jeweiligen Vorstand bestätigt wurde. In ▶ **Tab. 1** sind die an der Leitlinienerstellung beteiligten Fachgesellschaften und andere Organisationen sowie deren mandatierte Vertreter aufgeführt. Stimmberechtigt in den Abstimmungsprozessen (Konsensusverfahren) waren nur die von den teilnehmenden Fachgesellschaften und Organisationen benannten Mandatsträger nach Offenlegung und Ausschluss von Interessenkonflikten. Die Leitlinie wurde unter direkter Beteiligung einer Patientenvertreterin erstellt. Frau Marion Gebhardt (Frauenselbsthilfe nach Krebs e. V.) war von Beginn an in die Erstellung der Leitlinie eingebunden und nahm mit eigenem Stimmrecht an den Konsensuskonferenzen teil.

▶ **Tab. 1** Beteiligte Fachgesellschaften und andere Organisationen.

beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)	Christian Dannecker
Deutsche Gesellschaft für Epidemiologie (DGEpi)	Stefanie Klug
Deutsche Gesellschaft für Virologie e. V. (GfV)	Thomas Iftner
Deutsche Gesellschaft für Pathologie e. V. (DGP)	Thomas Löning Lars Horn (Stellvertreter) Dietmar Schmidt (Stellvertreter)
Deutsche STI-Gesellschaft e. V. (DSTIG)	Hans Ikenberg
Deutsche Gesellschaft für Zytologie (DGZ)*	Heinrich Neumann (bis 14.08.2013) Volker Schneider (bis 12.05.2014)
Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e. V. (GMDS)	Uwe Siebert Willi Sauerbrei (Stellvertreter)
Arbeitsgemeinschaft für gynäkologische Onkologie der DKG, AGO	Matthias Beckmann
Frauenselbsthilfe nach Krebs e. V.	Marion Gebhardt Heidemarie Haase (Stellvertreterin)
Berufsverband der Frauenärzte e. V., BVF*	Manfred Steiner Ulrich Freitag (Stellvertreter)
Arbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe e. V. (BLFG)	Michael Friedrich
Berufsverband zytologisch tätiger Ärzte in Deutschland e. V. (AZÄD)*	Klaus Neis Bodo Jordan (Stellvertreter)
Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der DGGG*	Wolfgang Kühn Michael Menton (Stellvertreter)
Arbeitsgemeinschaft Prävention und integrative Onkologie (PRIO), DKG Sektion B	Karsten Münstedt
HPV-Management-Forum (Paul-Ehrlich-Gesellschaft für Chemotherapie PEG e. V.)	Achim Schneider Andreas Kaufmann (Stellvertreter)
Studiengruppe Kolposkopie e. V.	K. Ulrich Petry
Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie der DGGG (AGII)	Axel P. A. Schäfer
DKFZ	Magnus von Knebel-Doeberitz (bis 25.06.2013) Michael Pawlita
internationale Organisationen	
Arbeitsgemeinschaft für gynäkologische Onkologie und Brustgesundheit (AGO) der (SGGG)**	Mathias Fehr
Arbeitsgemeinschaft für gynäkologische Onkologie (AGO) der (OEGGG)**	Christoph Grimm Olaf Reich (Stellvertreter)
European Society of Gynaecological Oncology (ESGO)***	Rainer Kimmig Martin Heubner (Stellvertreter)

* AG-CPC, AZÄD, BVF und DGZ traten am 12.05.2014 von der Mitarbeit an der Leitlinie zurück. Nach den konstruktiven Diskussionen in der Ad-hoc-Kommission ist der BVF der Leitliniengruppe am 04.09.2017 wieder beigetreten.

** Die internationalen Fachgesellschaften nahmen ohne Stimmrecht im Konsensusprozess teil.

*** Die ESGO hat zwar einen Mandatsträger und einen Stellvertreter benannt, diese haben sich jedoch nicht an der Leitlinienarbeit beteiligt.

II Leitlinienverwendung

Fragen und Ziele

Durch die Etablierung dieser S3-Leitlinie wird zum einen eine wichtige Forderung des Nationalen Krebsplans zum Zervixkarzinom-Screening erfüllt. Zum anderen kann die S3-Leitlinie wesentliche Informationen und Hilfestellungen für das geplante organisierte Zervixkarzinomscreening in Deutschland geben.

Die Ziele der alten S2k-Leitlinie „Prävention, Diagnostik und Therapie der HPV-Infektion und präinvasiver Läsionen des weiblichen Genitale“ werden fokussiert auf den Gebärmutterhals. Leitlinienempfehlungen zur primären Prävention werden aus der aktualisierten S3-Leitlinie „082/002 Impfprävention HPV-assoziierter Neoplasien“ übernommen, allerdings ergänzt bezüglich der Auswirkungen, die eine HPV-Impfung auf das Screening haben kann. Die 2014 fertig gestellte S3-Leitlinie „032/033OL Zervixkarzinom: Diagnostik, Therapie und Nachsorge“ umfasst alle Aspekte des invasiven Zervixkarzinoms.

Versorgungsbereich

Diese S3-Leitlinie zur Prävention des Zervixkarzinoms legt die Aspekte zur Prävention des Zervixkarzinoms und zu Diagnostik, Therapie und Nachsorge bis einschließlich der hochgradigen präinvasiven Läsionen dar. Wesentliche Ziele der Leitlinie sind die Analyse der vorhandenen Daten nach Optimierung der Krebsfrüherkennung des Zervixkarzinoms hinsichtlich der Testverfahren, der Organisationsstruktur, des Abklärungsalgorithmus, der Therapie und die Klärung der Frage, wie die Vorsorgeverweigererinnen zur Teilnahme stimuliert werden können. Daneben gilt es, die Auswirkung der HPV-Impfung auf die Krebsfrüherkennung-Strategie zu untersuchen.

Patienten/innenzielgruppe

Diese S3-Leitlinie richtet sich an alle Frauen ab einem Alter von 20 Jahren.

Anwenderzielgruppe/Adressaten

Die Empfehlungen der Leitlinie richten sich an alle Ärzte und Angehörigen von Berufsgruppen, die mit der Früherkennung des Zervixkarzinoms befasst sind, vor allem an Gynäkologen, Pathologen bzw. Zytologen, sowie alle Mitarbeiter von Dysplasiesprechstunden und -zentren.

Weitere Adressaten sind:

- medizinisch-wissenschaftliche Fachgesellschaften und Berufsverbände, die mit der Früherkennung des Zervixkarzinoms befasst sind,
- Interessenvertretungen von Frauen (Frauengesundheitsorganisationen, Patienten- und Selbsthilfeorganisationen),
- Qualitätssicherungseinrichtungen und -projekte auf Bundes- und Länderebene,
- gesundheitspolitische Einrichtungen und Entscheidungsträger auf Bundes- und Länderebene,
- Kostenträger,
- die Öffentlichkeit zur Information über gute medizinische Vorgehensweise.

Verabschiedung und Gültigkeitsdauer

Diese Leitlinie besitzt eine Gültigkeitsdauer vom 31.12.2017 bis 31.12.2020. Diese Dauer ist aufgrund der inhaltlichen Zusammenhänge geschätzt. Der Bedarf zur Aktualisierung der Leitlinie ergibt sich zudem aus der Existenz neuer wissenschaftlicher Erkenntnisse und der Weiterentwicklung in der Leitlinienmethodik. Zudem ist in regelmäßigen Abständen eine redaktionelle und inhaltliche Prüfung und Überarbeitung der Kernaussagen und Empfehlungen der Leitlinie erforderlich.

III Leitlinienmethodik

Grundlagen

Die Methodik zur Erstellung dieser Leitlinie wird durch die Vergabe der Stufenklassifikation vorgegeben. Das AWMF-Regelwerk (Version 1.0) gibt entsprechende Regelungen vor. Es wird zwischen der niedrigsten Stufe (S1), der mittleren Stufe (S2) und der höchsten Stufe (S3) unterschieden. Die niedrigste Klasse definiert sich durch eine Zusammenstellung von Handlungsempfehlungen, erstellt durch eine nicht repräsentative Expertengruppe. Im Jahr 2004 wurde die Stufe S2 in die systematische evidenzrecherchebasierte (S2e) oder strukturelle konsensbasierte Unterstufe (S2k) gegliedert. In der höchsten Stufe S3 vereinigen sich beide Verfahren. Diese Leitlinie entspricht der Stufe: S3.

Evidenzgraduierung

Zur Graduierung der identifizierten Studien wurde in dieser Leitlinie das von der GRADE Working Group [1] (www.gradeworkinggroup.org) entwickelte System (GRADE = Grading of Recommendations Assessment, Development and Evaluation) angewendet (▶ **Tab. 2**).

▶ **Tab. 2** Schema der Evidenzgraduierung nach GRADE.

GRADE	Beschreibung	Symbol
hohe Qualität	Wir sind uns sehr sicher, dass der wahre Effekt nah an der Schätzung liegt. *„We are very confident that the true effect lies close to that of the estimate of the effect.“*	⊕⊕⊕⊕
moderate Qualität	Wir sind uns relativ sicher mit der Abschätzung des Effekts: Der wahre Effekt liegt wahrscheinlich nah an der Schätzung, allerdings besteht auch die Möglichkeit eines substanziellen Unterschieds. *„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.“*	⊕⊕⊕⊖
niedrige Qualität	Unser Vertrauen in den Effektschätzer ist eingeschränkt: Der wahre Effekt könnte sich substanziell vom Effektschätzer unterscheiden. *„Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.“*	⊕⊕⊖⊖
sehr niedrige Qualität	Wir haben nur sehr geringes Vertrauen in den Effektschätzer: Der wahre Effekt unterscheidet sich wahrscheinlich substanziell vom Effektschätzer. *„We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.“*	⊕⊖⊖⊖

Empfehlungsgraduierung

Die Methodik des Leitlinienprogramms Onkologie sieht eine Vergabe von Empfehlungsgraden durch die Leitlinienautoren im Rahmen eines formalen Konsensusverfahrens vor. Dementsprechend wurden strukturierte Konsensuskonferenzen durchgeführt [2] (Details im Leitlinienreport). Im Rahmen dieser Prozesse wurden die Empfehlungen von den stimmberechtigten Mandatsträgern formal abgestimmt.

In der Leitlinie werden zu allen evidenzbasierten Statements und Empfehlungen Angaben zur Evidenzgraduierung der zugrunde liegenden Studien sowie bei Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in dieser Leitlinie entsprechend dem AWMF-Regelwerk [2] 3 Empfehlungsgrade unterschieden, die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln (▶ **Tab. 3**).

Die Entscheidungskriterien für die Festlegung der Empfehlungsgrade werden im Leitlinienreport zu dieser Leitlinie erläutert.

▶ **Tab. 3** Schema der Empfehlungsgraduierung.

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Statements

Als Statements werden Darlegungen oder Erläuterungen von spezifischen Sachverhalten oder Fragestellungen ohne unmittelbare Handlungsaufforderung bezeichnet. Sie werden entsprechend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens verabschiedet und können entweder auf Studienergebnissen oder auf Expertenmeinungen beruhen (▶ **Tab. 4**).

▶ **Tab. 4** Konsensstärke.

Konsensstärke	prozentuale Zustimmung
starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75–95 % der Stimmberechtigten
mehrheitliche Zustimmung	> 50–75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Expertenkonsens (EK)

Statements/Empfehlungen, für die eine Bearbeitung auf der Grundlage von Expertenkonsens der Leitliniengruppe beschlossen wurde, sind als Expertenkonsens ausgewiesen. Für die Graduierung der Expertenkonsens wurden keine Symbole bzw. Buchstaben verwendet, die Stärke des Konsenspunktes ergibt sich aus der verwendeten Formulierung (soll/sollte/kann) entsprechend der Abstufung in ▶ **Tab. 3**.

IV Leitlinie

1 Differenzialdiagnostik und Abklärungsalgorithmus

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.1.	Bei einem zytologischen Befund der Gruppe IIa sollte der behandelnde Gynäkologe darauf hingewiesen werden, dass in der Vergangenheit (2 Jahre) ein auffälliger Befund vorlag und die Patientin weiterhin beobachtet werden soll. Weitere differenzialdiagnostische Abklärungen sollen nur dann indiziert werden, wenn dies aufgrund der aktuellen Konstellation notwendig ist, um eine Überbehandlung zu vermeiden.	EK	

1.1 Indikation zur Koloskopie in Abhängigkeit der Wahrscheinlichkeit für eine CIN 3

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.2.	Die Indikation zur kolposkopischen Abklärung sollte ab einer Post-Test-Wahrscheinlichkeit für ein durchschnittliches kumulatives CIN-3+-Risiko von 10 % gestellt werden.	EK	

1.2 Welche Abklärungsmethoden sind geeignet bei auffälliger Zytologie?

1.2.1 Grenzwertige zytologische Auffälligkeiten (Pap II-p, II-g)

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.3.	Bei Befunden der Gruppe II-p ~ ASC-US und II-g ~ AGUS im organisierten zytologischen Screening sollte ein HR-HPV-Test in 6 Monaten durchgeführt werden. Ist dieser HR-HPV-Test positiv, sollte eine kolposkopische Abklärung innerhalb von 3 Monaten erfolgen. Bei HPV-Negativität sollte eine zytologische und HPV-Kontrolle nach 12 Monaten durchgeführt werden.	⊕⊕⊕⊖ B	[3 – 53]
10.4.	Bei Befunden der Gruppe II-p ~ ASC-US und II-g ~ AGUS im organisierten zytologischen Screening kann eine p16/Ki-67-Testung in 6 Monaten durchgeführt werden. Ist dieser p16/Ki-67-Nachweis positiv, sollte eine kolposkopische Abklärung innerhalb von 3 Monaten erfolgen. Bei p16/Ki-67-Negativität sollte eine zytologische und HPV-Kontrolle nach 12 Monaten durchgeführt werden.	⊕⊖⊖⊖ 0	[43, 54 – 56]

1.2.2 Zytologischer Verdacht auf leichte Dysplasie (Pap IIID1)

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.5.	Bei Befunden der Gruppe IIID1 ~ LSIL im organisierten zytologischen Screening sollte eine Abklärung mittels HR-HPV-Test in 6 Monaten erfolgen. Ist dieser HR-HPV-Test positiv, sollte eine kolposkopische Abklärung innerhalb von 3 Monaten erfolgen. Bei HPV-Negativität sollte eine zytologische und HPV-Kontrolle nach 12 Monaten durchgeführt werden.	⊕⊕⊕⊖ B	[4, 5, 8, 10, 13, 17, 23, 26 – 29, 31, 32, 35, 39, 41 – 43, 45 – 49, 51 – 53, 57 – 68]
10.6.	Bei Befunden der Gruppe IIID1 ~ LSIL im organisierten zytologischen Screening kann eine Abklärung mittels p16/Ki-67-Testung in 6 Monaten erfolgen. Ist dieser p16/Ki-67-Nachweis positiv, sollte eine kolposkopische Abklärung innerhalb von 3 Monaten erfolgen. Bei p16/Ki-67-Negativität sollte eine zytologische und HPV-Kontrolle nach 12 Monaten durchgeführt werden.	⊕⊖⊖⊖ 0	[43, 55, 56, 68, 69]

1.2.3 Unklare zytologische Befunde mit Pap III-p, III-g, III-x

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.7.	a) Bei Befunden der Gruppe III-p, III-x, III-e oder III-g im organisierten zytologischen Screening kann eine Abklärung mittels HR-HPV-Test oder p16/Ki-67-Immunzytochemie innerhalb von 3 Monaten erfolgen. Ist dieser HR-HPV-Test oder der p16/Ki-67-Nachweis positiv, sollte eine kolposkopische Abklärung innerhalb von 3 Monaten erfolgen. Bei Negativität der Abklärungstests sollte eine zytologische und HPV-Kontrolle nach 12 Monaten durchgeführt werden. b) Bei Befunden der Gruppe III-x, III-e und III-g sollte eine endometriumsspezifische Abklärung zum Ausschluss einer endometrialen Neoplasie erfolgen (Vaginalsonografie, Hysteroskopie, fraktionierte Abrasio etc.).	EK	

1.2.4 Mittel- und höhergradige zytologische Auffälligkeiten (Pap IIID2, Pap IVa, Pap IVb, Pap V)

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.8.	Bei Befunden der Gruppen IIID2, IVa–p, IVa–g, IVb–p, IVb–g, V-p, V-g, V-e und V-x im organisierten zytologischen Screening soll eine kolposkopische Abklärung erfolgen.	EK	

1.3 Welche Abklärungsmethoden sind geeignet bei positivem HPV-Test im Screening > 30 Jahre?

Nr.	Empfehlungen/Statements	GRADE	Quellen
10.9.	Bei einem positiven HPV-Screeningtest sollte eine weiterführende zytologische Abklärung erfolgen.	⊕⊕⊖⊖ B	[70 – 79]
10.10.	Bei einem positiven HPV-Screeningtest kann eine weiterführende Abklärung mittels p16/Ki-67-Testung erfolgen.	⊕⊖⊖⊖ 0	[72, 73]
10.11.	Bei einem positiven HPV-16/18 Testergebnis im HPV-basierten Screening sollte eine kolposkopische Abklärung erfolgen.	⊕⊖⊖⊖ B	[77, 79]
10.12.	Bei einem positiven HPV-Screeningtest und einem Befund ab II-p in der Abklärungszytologie bzw. im kombinierten HPV-Pap-Screening sollte eine kolposkopische Abklärung erfolgen.	EK	

2 Kolposkopie

2.1 Einsatz der Abklärungskolposkopie

Nr.	Empfehlungen/Statements	GRADE	Quellen
11.1.	Die Kolposkopie soll nicht als Screeningmethode eingesetzt werden.	EK	
11.2.	Bei hohem Verdacht auf CIN 3+ bzw. ACis/Adeno-Ca (Risiko ≥ 10 %*) soll eine Abklärungskolposkopie durchgeführt werden, ▪ zur histologischen Sicherung von squamösen und glandulären Atypien/Neoplasien, ▪ zur Festlegung der operativen Strategie.	EK	
11.3.	Bei der Abklärungskolposkopie sollten bei Typ 1 und Typ 2 TZ kolposkopisch gesteuerte Biopsien aus der/den schwerstgradigen Läsion/en entnommen werden, bei Typ 3 TZ sollte eine endozervikale Curettage erfolgen.	EK	

* Post-Test-Wahrscheinlichkeit

2.2 Qualitätsmerkmale einer Abklärungskolposkopie bzw. einer Dysplasiesprechstunde

Nr.	Empfehlungen/Statements	GRADE	Quellen
11.4.	Die Kolposkopie soll als Abklärungskolposkopie in einer gemäß den Anforderungen der DKG/DGGG/AGO/AG-CPC/EFC zertifizierten Dysplasiesprechstunde/Dysplasieeinheit erfolgen.	EK	

3 Versorgungsstrukturen

Nr.	Empfehlungen/Statements	GRADE	Quellen
12.1.	An der seit 1971 empfohlenen Krebsfrüherkennungsuntersuchung (KFU) des Gebärmutterhalskrebses in Deutschland beteiligen sich jährlich ca. 50 % der Frauen. Rund 70 % der Frauen beteiligten sich an der Vorsorge mindestens einmal innerhalb eines 3-jährlichen Intervalls.	EK	
12.2.	Bei der deutschen Zervixkarzinom-Krebsfrüherkennungsuntersuchung (KFU) weisen Frauen mit niedrigem Sozialstatus und/oder hohem Alter eine geringere Teilnahmerate auf.	EK	
12.3.	Ein organisiertes Screening mit populationsbasierter Einladung und stringenter Qualitätssicherung kann zu einer effektiveren und sozial- wie altersbezogen ausgewogeneren Vorsorge führen.	EK	

4 Strategie bei Nichtinanspruchnahme der Vorsorge

4.1 Einladungsschreiben

Nr.	Empfehlungen/Statements	GRADE	Quellen
13.1.	Wiederholte Einladungsschreiben im Rahmen eines organisierten Screenings erhöhen die Teilnahmerate von den Frauen, welche die reguläre Früherkennungsuntersuchung nicht in Anspruch genommen haben, geringfügig.	⊕⊕⊖⊖	[80 – 84]

4.2 HPV-Selbstabnahme

Nr.	Empfehlungen/Statements	GRADE	Quellen
13.2.	Mit dem HPV-Selbstabstrich lässt sich die Teilnahmerate bei den Frauen verdoppeln, die mittels Einladung nicht an der Krebsfrüherkennung teilgenommen haben.	⊕⊕⊕⊖ B	[85 – 94]
13.3.	Diesen Frauen (Non-Respondern) sollte daher die Möglichkeit zum Selbstabstrich gegeben werden.	⊕⊕⊕⊖ B	[85 – 94]
13.4.	Der HPV-Selbstabstrich im Screening soll den Frauen vorbehalten bleiben, die sich nicht an der Krebsvorsorgeuntersuchung beteiligen.	⊕⊕⊕⊖ A	[89, 95 – 127]

5 Therapie

5.1 Geeignete Therapieverfahren für die Behandlung der squamösen und glandulären zervikalen intraepithelialen Neoplasien

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.1.	Schlingenexzision und Laserexzision sollen die Methoden der Wahl für die Behandlung der squamösen und glandulären zervikalen intraepithelialen Neoplasie sein.	⊕⊖⊖⊖ A	[128 – 130]
14.2.	Die Messerkonisation kann bei der Behandlung glandulärer intraepithelialer Neoplasien als Alternative gewählt werden.	⊕⊖⊖⊖ 0	[128]
14.3.	Die Laservaporisation zur Behandlung von CIN 1, CIN 2 oder CIN 3 soll nach histologischer Abklärung durch Knipsbiopsien nur durchgeführt werden, wenn alle folgenden Bedingungen erfüllt sind: ▪ die komplette Transformationszone ist einsehbar (T-Zone Typ 1), ▪ kein Anhalt für Veränderungen des Drüsenepithels, ▪ kein Anhalt für ein invasives Geschehen, ▪ keine Diskrepanz zwischen zytologischer, kolposkopischer und histologischer Einschätzung der Biologie der Veränderung, ▪ die Patientin ist nicht älter als 50 Jahre.	EK	

5.2 Therapie unter kolposkopischer Kontrolle

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.4.	Eine Therapie, ob Exzisions- oder Ablationsverfahren, soll unter kolposkopischer Kontrolle erfolgen.	EK	

5.3 Management der CIN

5.3.1 Abwarten, Kontrolle oder Therapie der CIN 1

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.5.	Bei histopathologisch gesicherter CIN 1 soll abgewartet und die Patientin nach 6 Monaten wieder evaluiert werden*.	EK	
14.6.	Wenn eine CIN 1 mit einer Pap-Gruppe IVa oder schwergradiger assoziiert ist und die Läsion kolposkopisch nicht adäquat beurteilbar ist und sich in die Endozervix ausdehnt, soll eine histopathologische Evaluierung des Endozervikalkanals erfolgen.	EK	

* Kommt eine exspektative Verlaufsbeobachtung oder ein rein ablatives Therapieverfahren zum Einsatz, wird empfohlen, dass eine kolposkopische Expertise mit einem positiven Vorhersagewert für CIN 2 oder CIN 3 von mindestens 65 % besteht [130].

5.3.2 Kontrolle oder Therapie der CIN 2

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.7.	Ist bei histopathologisch gesicherter CIN 2 durch komplettes Einsehen der Platten-Zylinderepithelgrenze die gesamte Läsion beurteilbar, soll abgewartet und die Patientin nach 6 Monaten wieder untersucht werden*.	EK	
14.8.	Ist die Platten-Zylinderepithelgrenze bei histopathologisch gesicherter CIN 2 nicht komplett einsehbar und/oder liegt mind. ein Pap IVa vor, soll eine histopathologische Evaluierung des Endozervikalkanals erfolgen.	EK	

* Kommt eine exspektative Verlaufsbeobachtung oder ein rein ablatives Therapieverfahren zum Einsatz, wird empfohlen, dass eine kolposkopische Expertise mit einem positiven Vorhersagewert für CIN 2 oder CIN 3 von mindestens 65 % besteht [130].

5.3.3 Therapie der CIN 3

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.9.	Die histopathologisch gesicherte CIN 3 soll entfernt werden.	EK	

5.3.4 Therapieempfehlungen für Adoleszentinnen

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.10.	Bei Frauen bis 24 Jahren mit histopathologisch gesicherter CIN 2 soll, bei CIN 3 kann eine konservative Strategie verfolgt werden, vorausgesetzt ▪ die Läsion ist in ihrer gesamten Ausdehnung kolposkopisch überwachbar und ▪ enthält keine atypische glanduläre Komponente und ▪ ein invasives Geschehen ist mit hoher Sicherheit ausgeschlossen. Bei Persistenz der CIN 2 für mehr als 24 Monate bzw. der CIN 3 für mehr als 12 Monate oder Ausdehnung der Läsion nach endozervikal sollte eine Therapie erfolgen. Die Therapie soll gewebeschonend durchgeführt werden*.	EK	
14.11.	Die konservative Behandlung der CIN 3 sollte bei Frauen bis 24 Jahren in einer zertifizierten Dysplasiesprechstunde (s. Kapitel 2 Kolposkopie) stattfinden.	EK	

* Kommt eine exspektative Verlaufsbeobachtung oder ein rein ablatives Therapieverfahren zum Einsatz, wird empfohlen, dass eine kolposkopische Expertise mit einem positiven Vorhersagewert für CIN 2 oder CIN 3 von mindestens 65 % besteht [130].

5.3.5 Exzisionsverfahren vs. Hysterektomie beim zervikalen Adenocarcinoma in situ (ACIS)

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.12.	Die definitive histopathologische Diagnose des ACIS (in Differenzialdiagnose zum invasiven Adenokarzinom) soll mittels eines Exzisionsverfahrens erfolgen. Für die definitive Behandlung des ACIS sollte bei abgeschlossener Familienplanung eine Hysterektomie durchgeführt werden. Bei nicht abgeschlossener Familienplanung soll eine Entfernung im Gesunden gefolgt von Nachbeobachtung mittels Kolposkopie, Zytologie und HPV-Nachweis erfolgen.	EK	

5.3.6 R0-Resektion und Vorgehen bei R1-Resektion

Nr.	Empfehlungen/Statements	GRADE	Quellen
14.13.	Die R0-Resektion der CIN 3 soll angestrebt werden.	EK	
14.14.	Bei einer R1-Situation nach chirurgischer Entfernung einer CIN 3 und fehlendem Verdacht auf ein invasives Karzinom soll primär die zytologische und HPV-basierte Nachkontrolle nach 6 Monaten erfolgen. Zeigen die Befunde der Nachbetreuung, dass eine Persistenz der CIN 3 vorliegt, soll erneut operiert werden.	EK	

6 Schwangerschaft

Nr.	Empfehlungen/Statements	GRADE	Quellen
15.1.	Die Indikationen einer Kolposkopie (und ggf. Biopsie) im Rahmen einer Schwangerschaft sind dieselben wie die außerhalb einer Schwangerschaft.	EK	
15.2.	Eine Abklärung auffälliger Gebärmutterhalskrebsscreening-Befunde sollte während einer Schwangerschaft in einer DKG/AG-CPC-zertifizierten Dysplasiesprechstunde stattfinden.	EK	
15.3.	Eine endozervikale Kürettage soll während einer Schwangerschaft nicht durchgeführt werden. Ein tiefer endozervikaler Abstrich sollte während einer Schwangerschaft nicht durchgeführt werden.	EK	
15.4.	Schließt die Abklärung (zytologisch, kolposkopisch, ggf. histologisch) das Vorliegen einer hochgradigen Dysplasie und eines Karzinoms aus, sind weitere kolposkopische und/oder zytologische Untersuchungen in der Schwangerschaft nicht erforderlich.	EK	

6.1 Vorgehen bei CIN 2/3 oder ACIS in der Schwangerschaft

Nr.	Empfehlungen/Statements	GRADE	Quellen
15.5.	Während einer Schwangerschaft soll bei einer CIN 2/3 oder einem ACIS keine operative Therapie erfolgen, wenn das Vorliegen eines invasiven Karzinoms mit hoher Sicherheit ausgeschlossen wurde.	EK	
15.6.	Während einer Schwangerschaft sollen bei einer CIN 2/3 oder einem ACIS kolposkopische Kontrollen erfolgen. Das Intervall sollte 3 Monate betragen.	EK	
15.7.	Nur wenn in der Schwangerschaft ein invasives Karzinom durch Zytologie, Kolposkopie und Biopsie nicht mit hoher Sicherheit ausgeschlossen werden kann, besteht die Indikation zur histologischen Abklärung durch ein Exzisionsverfahren.	EK	

6.2 Geburtsmodus bei CIN 2/3

Nr.	Empfehlungen/Statements	GRADE	Quellen
15.8.	Das Vorliegen einer CIN 2/3 soll keinen Einfluss auf die Entscheidungsfindung hinsichtlich des Geburtsmodus haben.	EK	

6.3 Geburtshilfliche Komplikationen nach CIN-Therapie

Nr.	Empfehlungen/Statements	GRADE	Quellen
15.9.	Exzisionsverfahren in der Schwangerschaft sind mit erheblichen geburtshilflichen Risiken wie Frühgeburt assoziiert. Vorangegangene Exzisionsverfahren sind auch für nachfolgende Schwangerschaften mit diesen Risiken assoziiert.	EK	
15.10.	Da die Messerkonisation mit dem höchsten geburtshilflichen Risiko assoziiert ist, soll sie bei Frauen mit noch nicht abgeschlossener Familienplanung nicht durchgeführt werden.	EK	

7 Nachbetreuung

7.1 HPV-Test und Zytologie in der Nachbetreuung nach Therapie einer CIN

Nr.	Empfehlungen/Statements	GRADE	Quellen
16.1.	In der Nachbetreuung nach Therapie einer CIN/ACIS soll eine kombinierte Untersuchung mit HPV-Test und Zytologie durchgeführt werden.	⊕⊕⊖⊖ A	[131 – 146]
16.2.	Bei auffälligen Befunden (mindestens 1 Testverfahren positiv) sollte eine differenzierte Kolposkopie durchgeführt werden.	⊕⊕⊖⊖ B	[131 – 146]

7.1.1 Zeitpunkt und Dauer der Nachbetreuung

Nr.	Empfehlungen/Statements	GRADE	Quellen
16.3.	Die kombinierte Nachbetreuungsuntersuchung mit HPV-Test und Zytologie sollte 6, 12 und 24 Monate nach Therapie erfolgen. Bei unauffälligen Befunden soll die Patientin weiterhin an den Vorsorgeuntersuchungen teilnehmen.	EK	

7.2 Stellenwert der Biomarker in der Nachbetreuung nach CIN-Therapie

7.2.1 Absetzungsrand als Prädiktor für ein Rezidiv einer therapierten CIN-Läsion

Nr.	Empfehlungen/Statements	GRADE	Quellen
16.4.	In der Nachbetreuung nach Therapie einer CIN/ACIS soll eine kombinierte Untersuchung mit HPV-Test und Zytologie durchgeführt werden.	⊕⊖⊖⊖	[134 – 136, 147 – 152]

7.2.2 Weitere Biomarker als Prädiktoren für ein Rezidiv einer therapierten CIN-2/3-Läsion

Nr.	Empfehlungen/Statements	GRADE	Quellen
16.5.	Biomarker (5-HPV-Typen mRNA, HPV-typenspezifische Persistenz) sollen in der Nachbetreuung von therapierten CIN-2/3-Läsionen nicht eingesetzt werden.	⊕⊖⊖⊖ A	[134, 137, 151, 153 – 157]

8 Komplementäre, alternative und integrative Medizin

8.1 Alternativmedizinische Diagnostik

Nr.	Empfehlungen/Statements	GRADE	Quellen
17.1.	Eine alternativmedizinische Diagnostik bei der Erkennung von Zervixdysplasien oder einer Disposition dazu soll nicht eingesetzt werden.	EK	

8.2 Alternativmedizinische Therapie

Nr.	Empfehlungen/Statements	GRADE	Quellen
17.2.	Die alternativmedizinische Therapie von Dysplasien sollte abgelehnt werden.	EK	

8.3 Komplementärmedizinische Therapie

Nr.	Empfehlungen/Statements	GRADE	Quellen
17.3.	Komplementärmedizinische Behandlungsempfehlungen lassen sich aufgrund des Mangels an aussagekräftigen Studien nicht aussprechen.	EK	

9 Aufklärung und Information, Umgang mit psychischer Belastung

9.1 Aufklärung und Information von Teilnehmerinnen an der Zervixkarzinomfrüherkennung

Nr.	Empfehlungen/Statements	GRADE	Quellen
18.1.	Bei der Aufklärung von Teilnehmerinnen an der Früherkennung des Zervixkarzinoms sollen folgende Aspekte berücksichtigt werden: ▪ Erklärung der Krankheit, ▪ natürlicher Infektionsverlauf bei HPV und der assoziierten Zellveränderungen, ▪ die verschiedenen HPV-Typen, ▪ Risikofaktoren für das Zervixkarzinom, ▪ Auswirkung auf Partner, ▪ Beschreibung der Früherkennungsmaßnahme, ▪ Angaben zu Nutzen und Schaden der Früherkennungsmaßnahme, ▪ Angaben zur Qualität der Früherkennungsmaßnahme.	EK	

9.2 Aufklärung über die Diagnose, Behandlungsmöglichkeiten und Nachbetreuung

Nr.	Empfehlungen/Statements	GRADE	Quellen
18.2.	Aufklärungsinhalte für Frauen mit abklärungsbedürftigem Screeningbefund sollen folgende Erläuterung enthalten: ▪ Befundergebnisse ▪ Differenzialdiagnostik ▪ Therapieoptionen ▪ angestrebte Behandlungsziele ▪ Dauer und die Durchführung der einzelnen Therapiemaßnahmen ▪ Notwendigkeit zur Nachbetreuung	EK	

10 Kosteneffektivität

Nr.	Empfehlungen/Statements	GRADE	Quellen
19.1.	Ein HPV-basiertes Screening alle 3 Jahre besitzt ein relativ günstiges Schaden-Nutzen-Verhältnis. Es erzeugt im Vergleich zum jährlichen zytologischen Screening einen vergleichbaren erwarteten Nutzen bei geringerem erwarteten Schaden (z. B. operative Eingriffe, Kolposkopien, psychische Belastung durch auffällige Befunde und Nachfolgeuntersuchungen).	⊕⊖⊖⊖	[s. Leitlinienreport und Evidenzbericht]
19.2.	Ein HPV-basiertes Screening mit Intervallen von 3–5 Jahren ist in Deutschland als kosteneffektiv zu bewerten. HPV-basierte Screeningverfahren mit Intervallen von 2 Jahren haben ein ungünstigeres Kosteneffektivitätsverhältnis. Screeningverfahren mit jährlichen Intervallen erhöhen deutlich die Kosten, ohne einen maßgeblichen Zusatznutzen zu generieren.	⊕⊖⊖⊖	[158]

Interessenkonflikt

Siehe Leitlinienreport: https://www.awmf.org/uploads/tx_szleitlinien/015-027OLm_Praevention_Zervixkarzinom_2018-01.pdf

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