

## 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



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### Key words

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

### Schlüsselwörter

Zervixkarzinom, zervikale intraepitheliale Neoplasie (CIN), zervikale Präkanzerosen, HPV

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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 pre-

cancerous 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/II/015-027OL.html> or [www.leitlinienprogramm-onkologie.de](http://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)
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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)
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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)
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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
<b>International organizations</b>	
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](http://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 $\geq 10\%^*$ ), diagnostic colposcopy must be carried out <ul style="list-style-type: none"> <li>▪ to histologically confirm squamous and glandular atypia/neoplasia,</li> <li>▪ to determine the surgical strategy.</li> </ul>	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 ( <i>Krebsfrüherkennungsuntersuchung</i> , 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: <ul style="list-style-type: none"> <li>the whole transformation zone can be visualized (T-Zone Type 1),</li> <li>there are no indications of any changes in the glandular epithelium,</li> <li>there are no indications of any invasive process,</li> <li>there are no discrepancies between cytological, colposcopic and histological assessments of the biology of any changes,</li> <li>the patient is not older than 50 years.</li> </ul>	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 <ul style="list-style-type: none"> <li>▪ the lesion can be evaluated colposcopically in its entirety, and</li> <li>▪ it does not contain any atypical glandular components, and</li> <li>▪ an invasive process can be excluded with a high degree of certainty.</li> </ul> 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: <ul style="list-style-type: none"> <li>▪ an explanation of the disease,</li> <li>▪ the natural progression of infection with HPV and associated cell changes,</li> <li>▪ the different HPV types,</li> <li>▪ the risk factors for cervical cancer,</li> <li>▪ the impact on the patient's partner(s),</li> <li>▪ a description of the screening method,</li> <li>▪ information about the benefits and harm of screening methods,</li> <li>▪ information on the quality of the screening methods.</li> </ul>	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: <ul style="list-style-type: none"> <li>▪ the findings</li> <li>▪ the differential diagnosis</li> <li>▪ the treatment options</li> <li>▪ the treatment goals</li> <li>▪ the duration of the different treatments and how they are carried out</li> <li>▪ the necessity of regular follow-up appointments</li> </ul>	EC	

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](https://www.awmf.org/uploads/tx_szleitlinien/015-027OLm_Praevention_Zervixkarzinom_2018-01.pdf)

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