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

Authors
Peter Hillemanns 1, Klaus Friese 2, Christian Dannecker 3, Stefanie Klug 4, Ulrike Seifert 5, Thomas Iftner 6, Juliane Hädicke 6, Thomas Lönig 7, Lars Horn 8, Dietmar Schmidt 9, Hans Ikenberg 10, Manfred Steiner 11, Ulrich Freitag 12, Uwe Siebert 13, 14, Gaby Sroczynski 13, Willi Sauerbrei 14, Matthias W. Beckmann 15, Marion Gebhardt 16, Michael Friedrich 17, Karsten Münstedt 18, Achim Schmeiser 19, Andreas Kaufmann 20, K. Ulrich Petry 21, Axel P. A. Schäfer 22, Michael Pawlita 23, Joachim Weiss 24, Anja Mehner 25, Mathias Fehr 26, Christoph Grimm 27, Olaf Reich 28, Marc Arbyn 29, Jos Kleijnen 30, Simone Wesselmann 31, Monika Nothacker 32, Markus Follmann 33, Thomas Langer 12, Matthias Jentschke 1

Affiliations
1 Klinik für Frauenheilkunde und Geburtshilfe, Medizinische Hochschule Hannover, Hannover, Germany
2 Klinik Bad Trissl GmbH, Oberaudorf, Germany
3 Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, München, Germany
4 Lehrstuhl für Epidemiologie, Technische Universität München, München, Germany
5 Tumorepidemiologie, Universitäts-Krebszentrum (UKZ), Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany
6 Institut für Medizinische Virologie und Epidemiologie der Viruskrankheiten, Universitätsklinikum Tübingen, Tübingen, Germany
7 Institut für Pathologie, Albertinen-Krankenhaus Hamburg, Hamburg, Germany
8 Institut für Pathologie, Universitätsklinikum Leipzig, Leipzig, Germany
9 Institut für Pathologie, Referenzzentrum für Gynäkopathologie, Mannheim, Germany
10 CytoMol – MVZ für Zytologie und Molekularbiologie, Frankfurt, Germany
11 Facharzt für Frauenheilkunde und Geburtshilfe, Ihringen, Germany
12 Facharzt für Frauenheilkunde und Geburtshilfe, Wismar, Germany
13 Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health, Health Services Research and Health Technology Assessment, UMIT – University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria
14 Institut für Med. Biometrie und Statistik (IMBI), Universitätsklinikum Freiburg, Freiburg, Germany
15 Frauenklinik, Universitätsklinikum Erlangen, Erlangen, Germany
16 Frauenseilbshilfe nach Krebs, Forchheim, Germany
17 Klinik für Frauenheilkunde und Geburtshilfe, Helios Klinikum Krefeld, Krefeld, Germany
18 Frauenklinik, Ortenau Klinikum Offenburg-Gengenbach, Offenburg, Germany
19 Medizinisches Versorgungszentrum im Fürstenberg-Karree, Berlin, Germany
20 Klinik für Gynäkologie, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, Berlin, Germany
21 Frauenklinik, Klinikum Wolfsburg, Wolfsburg, Germany
22 Facharzt für Frauenheilkunde und Geburtshilfe, Berlin, Germany
23 Deutsches Krebsforschungszentrum, Heidelberg, Germany
24 Klinik für Tumorbiologie, Klinik für Onkologische Rehabilitation – UKF Reha gGmbH, Freiburg, Germany
25 Abteilung für Medizinische Psychologie und Medizinische Soziologie, Universitätsklinikum Leipzig, Leipzig, Germany
26 Gynäkologie und Geburtshilfe in Frauenfeld, Spital Thurgau AG, Frauenfeld, Switzerland
27 Privatklinik Döbling, Wien, Austria
28 Privatklinik Graz Ragnitz, Graz, Austria
29 Cancer Center, Sciensano, Brüssel, Belgium
30 Kleijnen Systematic Reviews Ltd, York, United Kingdom
31 Deutsche Krebsgesellschaft, Berlin, Germany
32 AWMF-Institut für Medizinisches Wissensmanagement, Marburg, Germany
33 Leitlinienprogramm Onkologie, Deutsche Krebsgesellschaft, Berlin, Germany
34 Division of Health Technology Assessment and Bioinformatics, ONCOTYROL – Center for Personalized Cancer Medicine, Innsbruck, Austria

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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., (GVV)] | 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 [Arbeitgegenschaft 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 “032/0330L 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.” | ⊕⊕⊙⊙ |

Hillemanns P et al. Prevention of Cervical... Geburtsh Frauenheilk 2019; 79: 160–176
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). According to 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. | ⊕⊕⊕⊖ B | [3–53] |
| 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 |
| 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. | ⊕⊕⊕⊖ 0 | [43, 54–56] |

1.1 Indication for coloscopy depends on probability of CIN 3

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)
### 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. | | |
| 11.2 | If there is a high suspicion of CIN 3+ or ACIS/adenocarcinoma (risk \( \geq 10\% \)^*), diagnostic colposcopy must be carried out  
- to histologically confirm squamous and glandular atypia/neoplasia,  
- to determine the surgical strategy. | | |
| 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. | | |

* 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. | | |

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. | | |
| 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. | | |
| 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. | | |

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. | | [85 – 94] |
| 13.3 | Self-sampling should therefore be offered to these women (nonresponders). | | [85 – 94] |
| 13.4 | HPV self-collection for screening must be reserved for those women who do not otherwise participate in cancer screening. | | [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    |         |

Hillemanns P et al. Prevention of Cervical... Geburtsh Frauenheilk 2019; 79: 160–176
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 | |

* 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 |
|-----|---------------------------|-------|---------|
| 14.11. | 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 | |

5.3.6 R0 resection and approach for R1 resection

| 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 | |

5.6 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. | ⊕⊕⊖⊖ | [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). | ⊕⊕⊖⊖ | [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.                                                                                              | ⊕⊖⊖⊖  | [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    |                                             |
## 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

### References

[1] Balshem H, Helfand M, Schunemann HJ et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64: 401–406

[2] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) – Ständige Kommission Leitlinien. AWMF-Regelwerk „Leitlinien“. 2012. Online: http://www.awmf.org/leitlinien/awmf-regelwerk.html; last access: 10.11.2015

[3] Manos MM, Kinney WK, Hurley LB et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. JAMA 1999; 281: 1605–1610

[4] Bergeron C, Jeannel D, Poveda J et al. Human papillomavirus testing in women with mild cytologic atypia. Obstet Gynecol 2000; 95 (6 Pt 1): 821–827

[5] Lytwyn A, Sellors JW, Mahony JB et al. Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. HPV Effectiveness in Lowgrade Paps (HELP) Study No. 1 Group. CMAJ 2000; 163: 701–707

[6] Shlay JC, Dunn T, Byers T et al. Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on papanicolaou smears. Obstet Gynecol 2000; 96: 410–416

[7] Morin C, Bairati I, Bouchard C et al. Managing atypical squamous cells of undetermined significance in Papanicolaou smears. J Reprod Med 2001; 46: 799–805

[8] Rebello G, Hallam N, Smart G et al. Human papillomavirus testing and the management of women with mildly abnormal cervical smears: an observational study. BMJ 2001; 322: 893–894

[9] Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: Baseline results from a randomized trial. J Natl Cancer Inst 2001; 93: 293–299

[10] Kulasingam SL, Hughes JP, Kiviat NB et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. JAMA 2002; 288: 1749–1757

[11] Pretorius RC, Belinson JL, Burchette RJ et al. Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. J Low Genit Tract Dis 2011; 15: 180–188

[12] Cuzick J, Szarewski A, Cubie H et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003; 362: 1871–1876

[13] Guoyt A, Karim S, Kyi MS et al. Evaluation of adjunctive HPV testing by Hybrid Capture II in women with minor cytological abnormalities for the diagnosis of CIN2/3 and cost comparison with colposcopy. BMC Infect Dis 2003; 3: 23

[14] Lonky NM, Felix JC, Naidu YM et al. Triage of atypical squamous cells of undetermined significance with hybrid capture II: colposcopy and histologic human papillomavirus correlation. Obstet Gynecol 2003; 101: 481–489

[15] Ordl J, Puig-Tintore LM, Torre A et al. Contribution of high risk human papillomavirus testing to the management of premalignant and malignant lesions of the uterine cervix. Med Clin (Barc) 2003; 121: 441–445

[16] Wensveen C, Kagie M, Veldhuizen R et al. Detection of cervical intraepithelial neoplasia in women with atypical squamous or glandular cells of undetermined significance cytology: a prospective study. Acta Obstet Gynecol Scand 2003; 82: 883–889

[17] Andersson S, Dillner L, Elf gren K et al. A comparison of the human papillomavirus test and Papanicolaou smear as a second screening method for women with minor cytological abnormalities. Acta Obstet Gynecol Scand 2005; 84: 996–1000

[18] Dalla Palma P, Pojer A, Girlando S. HPV triage of women with atypical squamous cells of undetermined significance: a 3-year experience in an Italian organized programme. Cytopathology 2005; 16: 22–26

[19] Davis-Denive S, Day SJ, Freund GG. Test performance comparison of in-form HPV and hybrid capture 2 high-risk HPV DNA tests using the SurePath liquid-based Pap test as the collection method. Am J Clin Pathol 2005; 124: 24–30

[20] Giovannelli L, Capra G, Lama A et al. Atypical squamous cells of undetermined significance–favour reactive compared to atypical squamous cells of undetermined significance–favour dysplasia: association with cervical intraepithelial lesions and human papillomavirus infection. J Clin Virol 2005; 33: 281–286

[21] Nieh S, Chen SF, Chu TY et al. Is p16(INK4A) expression more useful than human papillomavirus test to determine the outcome of atypical squamous cells of undetermined significance–categorized Pap smear? A comparative analysis using abnormal cervical smears with follow-up biopsies. Gynecol Oncol 2005; 97: 35–40

[22] Bergeron C, Cas F, Fagnani F et al. [Assessment of human papillomavirus testing on liquid-based Cyto-screen system for women with atypical squamous cells of undetermined significance. Effect of age]. Gynecol Obstet Fertil 2006; 34: 312–316

[23] Holladay EB, Logan S, Arnold J et al. A comparison of the clinical utility of p16(INK4A) immunolocalization with the presence of human papillomavirus by hybrid capture 2 for the detection of cervical dysplasia/neo- plasia. Cancer 2006; 108: 451–461
Kelly D, Kincaid E, Fansler Z et al. Detection of cervical high-grade squamous intraepithelial lesions from cytologic samples using a novel immunocytochemical assay (ProEx C). Cancer 2006; 108: 494–500

Kiatpongsan S, Niranthsar S, Mutirangura A et al. Role of human papillomavirus DNA testing in management of women with atypical squamous cells of undetermined significance. Int J Gynecol Cancer 2006; 16: 262–265

Monsonego J, Pintos J, Semaille C et al. Human papillomavirus testing improves the accuracy of colposcopy in detection of cervical intraepithelial neoplasia. Int J Gynecol Cancer 2006; 16: 591–598

Ronco G, Cucic J, Segnan N et al. HPV triage for low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology. Eur J Cancer 2007; 43: 476–480

De Francesco MA, Gargiulo F, Schreiber C et al. Comparison of the AMPLICOR human papillomavirus test and the hybrid capture 2 assay for detection of high-risk human papillomavirus in women with abnormal PAP smear. J Virol Methods 2008; 147: 10–17

Monsonego J, Pollini G, Evrad M et al. Detection of human papillomavirus genotypes among high-risk women: a comparison of hybrid capture and linear array tests. Sex Transm Dis 2008; 35: 521–527

Siddiqui MT, Homaran K, Cohen C et al. ProEx C immunocytochemistry and high-risk human papillomavirus DNA testing in papanicolaou tests with atypical squamous cell (ASC-US) cytology: correlation study with histologic biopsy. Arch Pathol Lab Med 2008; 132: 1648–1652

Szarewski A, Ambroisine L, Cadman L et al. Comparison of predictors for high-grade cervical intraepithelial neoplasia in women with abnormal smears. Cancer Epidemiol Biomarkers Prev 2008; 17: 3033–3042

Cattani P, Zannoni GF, Ricci C et al. Clinical performance of human papillomavirus E6 and E7 mRNA testing for high-grade lesions of the cervix. J Clin Microbiol 2009; 47: 3895–3901

Silverfo I, Andrade B, Wilander E. Value of high-risk HPV-DNA testing in the triage of ASCUS. Acta Obstet Gynecol Scand 2009; 88: 1006–1010

Del Mistro A, Frayle-Salamanca H, Trevisan R et al. Triage of women with atypical squamous cells of undetermined significance (ASC-US): results of an Italian multicentric study. Gynecol Oncol 2010; 117: 77–81

Denton KJ, Bergeron C, Klempt PT et al. The sensitivity and specificity of p16(NK4)4 cytology vs. HPV testing for detecting high-grade cervical disease in the triage of ASC-US and LSIL pap cytology results. Am J Clin Pathol 2010; 134: 12–21

Haffon P, Benmoua D, Agostini A et al. Stepwise algorithm combining HPV high-risk DNA-based assays and RNA-based assay for high grade CIN in women with abnormal smears referred to colposcopy. Cancer BioMark 2010; 7: 133–139

Alameda F, Pijuan L, Lloveras B et al. The value of p16 in ASCUS cases: a retrospective study using frozen cytologic material. Diagn Cytopathol 2011; 39: 110–114

Belinson JL, Wu R, Belinson SE et al. A population-based clinical trial comparing endocervical high-risk HPV testing using hybrid capture 2 and Cervista from the SHENCCST II Study. Am J Clin Pathol 2011; 135: 790–795

Clad A, Reuschenbach M, Weinschenk J et al. Performance of the Aptima high-risk human papillomavirus mRNA assay in a referral population in comparison with Hybrid Capture 2 and cytology. J Clin Microbiol 2011; 49: 1071–1076

Dufresne S, Sauthier P, Mayrand MH et al. Human papillomavirus (HPV) DNA triage of women with atypical squamous cells of undetermined significance with Amplicor HPV and Hybrid Capture 2 assays for detection of high-grade lesions of the uterine cervix. J Clin Microbiol 2011; 49: 48–53

Monsonego J, Hudgens MG, Zerat L et al. Evaluation of oncogenic human papillomavirus RNA and DNA tests with liquid-based cytology in primary cervical cancer screening: the FASE study. Int J Cancer 2011; 129: 691–701

Ratnam S, Coutlée F, Fontaine D et al. Aptima HPV E6/E7 mRNA test is as sensitive as Hybrid Capture 2 Assay but more specific at detecting cervical precancer and cancer. J Clin Microbiol 2011; 49: 557–564

Schmidt D, Bergeron C, Denton KJ et al. p16/Ki-67 dual-stain cytology in the triage of ASCUS and LSIL papanicolaou cytology: results from the European equivocal or mildly abnormal Papanicolaou cytology study. Cancer Cytopathol 2011; 119: 158–166

Stoler MH, Wright TC jr., Sharma A et al. High-risk human papillomavirus testing in women with ASC-US cytology: results from the ATHENA HPV study. Am J Clin Pathol 2011; 135: 468–475

Szarewski A, Mesher D, Cadman L et al. Comparison of seven tests for high-grade cervical intraepithelial neoplasia in women with abnormal smears: the Predictors 2 study. J Clin Microbiol 2012; 50: 1867–1873

Alakhebandan R, Fontaine D, Bentley J et al. Performance of ProEx C and PreTect HPV-Proofer E6/E7 mRNA tests in comparison with the hybrid capture 2 HPV DNA test for triaging ASCUS and LSIL cytology. Diagn Cytopathol 2013; 41: 767–775

Olivera A, Verdasc N, Pista A. Use of the NuClISENS Easy HPV qPCR in the management of cervical intraepithelial neoplasia. J Med Virol 2013; 85: 1235–1241

Denise Zielinski G, Snijders PJF, Rozendaal L et al. High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance. J Pathol 2001; 195: 300–306

Chen HS, Su TH, Yang YC et al. Human Papillomavirus Testing (Hybrid Capture II) to Detect High-Grade Cervical Intraepithelial Neoplasia in Women with Mildly Abnormal Papanicolaou Results. Taiwanese Journal of Obstetrics and Gynecology 2005; 44: 252–257

Cuscieri KS, Graham C, Moore C et al. Human Papillomavirus testing for the management of low-grade cervical abnormalities in the UK–Influence of age and testing strategy. J Clin Virol 2007; 38: 14–18

You K, Liang X, Qin F et al. High-risk human papillomavirus DNA testing and high-grade cervical intraepithelial lesions. Aust N Z J Obstet Gynaecol 2007; 47: 141–144

Huang S, Erickson B, Tang N et al. Clinical performance of Abbott Real-Time High Risk HPV test for detection of high-grade cervical intraepithelial neoplasia in women with abnormal cytology. J Clin Virol 2009; 45 (Suppl. 1): 519–523

Lee JK, Kim MK, Song SH et al. Comparison of Human Papillomavirus Detection and Typing by Hybrid Capture 2, Linear Array, DNA Chip, and Cycle Sequencing in Cervical Swab Samples. Int J Gynecol Cancer 2009; 19: 266–272

Edgerton N, Cohen C, Siddiqui MT. Evaluation of CINtec PLUS® test as an adjunctive test in ASC-US diagnosed SurePath® preparations. Diagn Cytopathol 2013; 41: 35–40

Wentzensen N, Schwartz L, Zuna RE et al. Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. Clin Cancer Res 2012; 18: 4154–4162

Loghavi S, Walters AF, Bose S. CINtec PLUS® dual immunostain: a triage tool for cervical pap smears with atypical squamous cells of undetermined significance and low grade squamous intraepithelial lesion. Diagn Cytopathol 2013; 41: 582–587

Lee NW, Kim D, Park JT et al. Is the human papillomavirus test in combination with the Papanicolaou test useful for management of patients with diagnoses of atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions? Arch Pathol Lab Med 2001; 125: 1453–1457

Pretorius RG, Peterson P, Novak S et al. Comparison of two signal-amplification DNA tests for high-risk HPV as an aid to colposcopy. J Reprod Med 2002; 47: 290–296
Castle PE, Fetterman B, Thomas Cox J et al. The age-specific relationships of cervical cancer to age, parity, and nulliparity. Obstet Gynecol 2002; 94: 102–107

Meyer JL, Hanlon DW, Andersen BT et al. Evaluation of p 16INK4a expression in ThinPrep cervical specimens with the CINtec p 16INK4a assay: correlation with biopsy follow-up results. Cancer 2007; 111: 83–92

Castle PE, Fetterman B, Thomas Cox J et al. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical pre-cancer and cancer. Obstet Gynecol 2010; 116: 76–84

Halford JA, Batty T, Boost T et al. Comparison of the sensitivity of conventional and ThinPrep Imaging System for 1,083 biopsy confirmed high-grade squamous lesions. Diagn Cytopathol 2010; 38: 318–326

Voss JS, Kipp BR, Campion MB et al. Assessment of fluorescence in situ hybridization and hybrid capture 2 analyses of cervical cytology specimens diagnosed as low grade squamous intraepithelial lesion for the detection of high grade cervical intraepithelial neoplasia. Anal Quant Cytol Histol 2010; 32: 121–130

Wu R, Belinson SE, Du H et al. Human papillomavirus messenger RNA assay for cervical cancer screening: the Shenzhen Cervical Cancer Screening Trial I. Int J Gynecol Cancer 2010; 20: 1411–1414

Heider A, Austin RM, Zhao C. HPV test results stratify risk for histopathologic follow-up findings of high grade cervical intra-epithelial neoplasia in women with low-grade squamous intra-epithelial lesion Pap results. Acta Cytol 2011; 55: 48–53

Levi AW, Harigopal M, Hui P et al. Use of high-risk human papillomavirus testing in patients with low-grade squamous intra-epithelial lesions. Cancer Cytopathol 2011; 119: 228–234

Tsoumpou I, Valasoulis G, Founta C et al. High-risk human papillomavirus DNA test and p16(INK4a) in the triage of LSIL: a prospective diagnostic study. Gynecol Oncol 2011; 121: 49–53

Heider A, Austin RM, Zhao C. HPV test results stratify risk for histopathologic follow-up findings of high grade cervical intra-epithelial neoplasia in women with low-grade squamous intra-epithelial lesion Pap results. Acta Cytol 2011; 55: 48–53

Tseng DS, Cox E, Plane MB et al. Efficacy of patient letter reminders on cervical cancer screening: a meta-analysis. J Gen Intern Med 2001; 16: 563–568

Stone EG, Morton SC, Hulscher ME et al. Interventions that increase use of adult immunization and cancer screening services: a systematic review. BMC Public Health 2013; 13: 464

Ferroni E, Camilloni L, Jimenez B et al. How to increase uptake in oncology screening: a systematic review of studies comparing population-based screening programs and spontaneous access. Prev Med 2012; 55: 587–596

Virtanen A, Nieminen P, Luostarinen T et al. Self-sample HPV tests as an alternative to HPV testing in primary cervical screening: the Shenzhen Cervical Cancer Screening Trial. Acta Cytol 2010; 54: 150–151

Gök M, Heideman DA, van Kemenade FJ et al. HPV testing on self-sampled cervicovaginal brushes: An effective alternative to protect nonresponders in cervical screening programs. Int J Cancer 2007; 120: 1505–1510

Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A et al. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): A community-based randomised controlled trial. The Lancet 2011; 378: 1868–1873

Szarewski A, Cadman L, Mesher D et al. HPV self-sampling as an alternative strategy in non-attenders for cervical screening – a randomised controlled trial. Br J Cancer 2011; 104: 915–920

Virtanen A, Nieminen P, Luostarinen T et al. Self-sample HPV tests as an intervention for nonattendees of cervical cancer screening in Finland: a randomized trial. Cancer Epidemiol Biomarkers Prev 2011; 20: 1960–1969

Gök M, van Kemenade FJ, Heideman DA et al. Experience with high-risk human papillomavirus testing on vaginal brush-based self-samples of non-attendees of the cervical screening program. Int J Cancer 2012; 130: 1228–1235
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Editors
Leading Professional Medical Associations

German Society of Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. [DGGG])
Head Office of DGGG and Professional Societies
Hausvogteiplatz 12, DE-10117 Berlin
info@dggg.de
http://www.dggg.de/

President of DGGG
Prof. Dr. med. Anton Scharl
Direktor der Frauenkliniken
Klinikum St. Marien Amberg
Mariahilfbergweg 7, DE-92224 Amberg
Kliniken Nordoberpfalz AG
Söllnerstraße 16, DE-92637 Weiden

DGGG Guidelines Representatives
Prof. Dr. med. Matthias W. Beckmann
Universitätsklinikum Erlangen, Frauenklinik
Universitätsstraße 21–23, DE-91054 Erlangen

Prof. Dr. med. Erich-Franz Solomayer
Universitätsklinikum des Saarlandes
Geburtshilfe und Reproduktionsmedizin
Kirrberger Straße, Gebäude 9, DE-66421 Homburg

Guidelines Coordination
Dr. med. Paul Gaß, Dr. med. Gregor Olmes, Christina Meixner
Universitätsklinikum Erlangen, Frauenklinik
Universitätsstraße 21–23, DE-91054 Erlangen
fk-dggg-leitlinien@uk-erlangen.de
http://www.dggg.de/leitlinienstellungnahmen

Austrian Society of Gynecology and Obstetrics (Österreichische Gesellschaft für Gynäkologie und Geburtshilfe [OEGGG])
Frankgasse 8, AT-1090 Wien
stephanie.leutgeb@oeggg.at
http://www.oeggg.at

President of OEGGG
Prof. Dr. med. Petra Kohlberger
Universitätsklinik für Frauenheilkunde Wien
Währinger Gürtel 18–20, AT-1090 Wien

OEGGG Guidelines Representatives
Prof. Dr. med. Karl Tamussino
Universitätsklinik für Frauenheilkunde und Geburtshilfe Graz
Auenbruggerplatz 14, AT-8036 Graz

Prof. Dr. med. Hanns Helmer
Universitätsklinik für Frauenheilkunde Wien
Währinger Gürtel 18–20, AT-1090 Wien

gynécologie suisse

Swiss Society of Gynecology and Obstetrics (Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe [SGGG])
Gynécologie Suisse SGGG
Altenbergstraße 29, Postfach 6, CH-3000 Bern 8
sekretariat@sggg.ch
http://www.sggg.ch/

President of SGGG
Dr. med. David Ehm
FMH für Geburtshilfe und Gynäkologie
Nägeligasse 13, CH-3011 Bern

SGGG Guidelines Representatives
Prof. Dr. med. Daniel Surbek
Universitätsklinik für Frauenheilkunde
Geburtshilfe und feto-maternale Medizin
Inselspital Bern
Effingerstraße 102, CH-3010 Bern

Prof. Dr. med. René Hornung
Kantonsspital St. Gallen, Frauenklinik
Rorschacher Straße 95, CH-9007 St. Gallen