

Registry Study of the Working Group on Cervical Pathology and Colposcopy (AGCPC) on the Diagnostic Algorithm for the New Cervical Cancer Screening – Initial Data

Registerstudie der Arbeitsgemeinschaft Zervixpathologie und Kolposkopie e. V. (AGCPC) zum Abklärungsalgorithmus im neuen Zervixkarzinom-Screening – erste Daten



Authors

Melanie Henes¹, Ellen Mann², Christine Hirchenhain³, Emanuel Bauer⁴, Alexander Kentner⁵, Jens Quaas⁶, Christopher Koßagk⁷, Julia Gallwas⁸, Leon Henes¹, Antonia Schumacher¹, Volkmar Küppers⁹ 

Affiliations

- 1 Department für Frauengesundheit Tübingen, Universitäts-frauenklinik, Tübingen, Germany
- 2 Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Rostock, Germany
- 3 Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany
- 4 amedes MVZ für Gynäkologie und Pathologie München, München, Germany
- 5 Klinik für Frauenheilkunde und Geburtshilfe, Erfurt, Germany
- 6 Facharztpraxis für Frauenheilkunde und Geburtshilfe, Hansestadt Stralsund, Germany
- 7 Gynäkologisches Versorgungszentrum Kreuzberg MVZ/Köpenick, Berlin, Germany
- 8 Klinik für Gynäkologie und Geburtshilfe, Universitätsmedizin Göttingen, Georg-August-Universität, Göttingen, Germany
- 9 Zytologisches Labor, Facharztpraxis für Frauenheilkunde und Geburtshilfe, Düsseldorf, Germany

Key words

cervical cancer screening, cancer screening guideline (oKFE-RL), co-test, diagnostic algorithm, cervical intraepithelial neoplasia, human papillomavirus (HPV)

Schlüsselwörter

Zervixkarzinom-Screening, Krebsfrüherkennungs-Richtlinie (oKFE-RL), Co-Test, Abklärungsalgorithmus, zervikale intraepitheliale Neoplasie, humanes Papillomavirus (HPV)

received 11.7.2023

accepted after revision 19.8.2023

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Geburtsh Frauenheilk 2023; 83: 1250–1262

DOI 10.1055/a-2159-7510

ISSN 0016-5751

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Priv.-Doz. Volkmar Küppers

Zytologisches Labor

Facharztpraxis für Frauenheilkunde und Geburtshilfe

Königsallee 64

40212 Düsseldorf, Germany

info@dysplasie-praxis.de



Deutsche Version unter:

<https://doi.org/10.1055/a-2159-7510>.

ABSTRACT

Introduction

For the first time since 1971, new regulations were introduced for cervical cancer screening as an organized cancer screening guideline (oKFE-RL) starting 1 January 2020. From the age of 20, a cytological smear test is performed annually, and from the age of 35, so-called co-testing (cytology and test for high-risk HPV) is performed every three years. In case of abnormalities, the algorithm is used as the basis for investigation. According to this diagnostic algorithm, even so-called low-risk groups receive early colposcopic evaluation. This approach has been heavily debated and serves as the basis for this registry study.

Methods

All patients who presented to the centers for a colposcopy as part of the diagnostic algorithm were included after signing an informed consent form. The following findings were obtained: Medical history, colposcopy, histology, and cytology findings, as well as possible therapies and their findings. The aim was to evaluate the frequency of the target lesions cervical intraepithelial neoplasia (CIN) 2+/CIN 3+ in the respective groups.

Result

A total of 4763 patients were enrolled in the study from July 2020 to October 2022. As a referral diagnosis, HPV persistence (HPV: human papillomavirus) with group I was determined in 23.9% (1139), HPV persistence with group II-a in 2.1% (100), II-p (ASC-US) in 11.2% (535), and II-g (AGC endocervical NOS) in 1.3% (64). III-p (ASC-H) and III-g (AGC endocervical favor neoplastic) were found in 9.4% (447) and 2.2% (107), respectively, IIID1 (LSIL) in 19% (906), IIID2 (HSIL, moderate dysplasia) in 18.9% (898), IVa-p (HSIL, severe dysplasia) in 10.7% (508), IVa-g (AIS) in 0.7% (31), IVb-p (HSIL with features suspicious for invasion) and IVb-g (AIS with features suspicious for invasion) in 0.3% (15), 0.1% (6), and 7 with suspected invasion V-p (squamous cell carcinoma)/V-g (endocervical adenocarcinoma) (0.1%). In the IVa-p group (HSIL, severe dysplasia), 67.7% had CIN 2+ and 56.5% had CIN 3+, adenocarcinoma in situ (AIS), and adenocarcinoma. If the histology of the excised tissue specifically based on the colposcope findings was also evaluated, CIN 2+ was found in 79.7% of cases, and CIN 3+ in 67.3% of cases. In IIID2 (HSIL, moderate dysplasia), CIN 2+ was detected in 50.9%, and CIN 3+/AIS in 28.3%. After evaluating patients who underwent surgery immediately, this increased to 53.0% for CIN 2+ and 29.3% for CIN 3+/AIS. In IIID1 (LSIL), CIN 2+ was detected in 27.4% and CIN 3+/AIS in 11.7%, and in II-p (ASC-US), CIN 2+ was detected in 23.4% and CIN 3+ and AIS in 10.8%, and in II-g (AGC endocervical NOS), CIN 2+ was detected in 34.4% and CIN 3+ in 23.4%. In the HPV persistence/II-a and I group, 21% showed CIN 2+, and 12.1% showed CIN 3+ and AIS, and 13% showed CIN 2+ and 5.9% showed CIN 3+ and AIS. In patients who were HPV-negative and had further diagnostics performed on the basis of cytologic smear alone, 27.9% had CIN 2+, and 14.1% had CIN 3 and AIS.

Discussion

In a synopsis of the present findings of our initial data of the registry study on the new cervical cancer screening, according to the organized early cancer screening guideline (oKFE-RL), we could show that the target lesion CIN 3+ and AIS is detected unexpectedly frequently in a not insignificant proportion, especially in the cytological low-risk group. Currently, we cannot answer whether this can reduce the incidence and mortality of cervical carcinoma, but this could be an initial indication of this and will be reviewed in further long-term evaluations.

ZUSAMMENFASSUNG

Einleitung

Erstmals seit 1971, wurde das Zervixkarzinom-Screening als organisierte Krebsfrüherkennungs-Richtlinie (oKFE-RL) ab 01.01.2020 neu geregelt. Ab einem Alter von 20 Jahren wird jährlich ein zytologischer Abstrich und ab 35 Jahren ein sogenanntes Co-Testing (Zytologie und Test auf HPV-High-Risk-Viren) alle 3 Jahre durchgeführt. Bei Auffälligkeiten wird entsprechend dem Algorithmus abgeklärt. Dieser Abklärungsalgorithmus definiert, dass auch sogenannte Niedrig-risikogruppe frühzeitig eine kolposkopische Beurteilung erhalten. Diese Vorgehensweise wurde stark diskutiert und dient als Grundlage dieser Registerstudie.

Methode

Alle Patientinnen, die sich im Rahmen des Abklärungsalgorithmus zur Kolposkopie in den Zentren vorgestellt hatten, wurden nach Einwilligung eingeschlossen. Folgende Befunde wurden erhoben: Anamnese, kolposkopische, histologische und zytologische Befunde sowie mögliche Therapien und deren Befund. Ziel war es, die Häufigkeit der Zielläsionen zervikale intraepitheliale Neoplasie (CIN) 2+/CIN 3+ in den jeweiligen Gruppen zu evaluieren.

Ergebnis

Von Juli 2020 bis Oktober 2022 wurden insgesamt 4763 Patientinnen in die Studie eingeschlossen. Als Zuweisungsdiagnose zeigte sich bei 23,9% (1139) eine HPV-Persistenz (HPV: humanes Papillomavirus) mit Gruppe I, bei 2,1% (100) eine HPV-Persistenz mit Gruppe II-a, bei 11,2% (535) ein II-p (ASC-US) und bei 1,3% (64) ein II-g (AGC endocervical NOS). Einen III-p (ASC-H) bzw. III-g (AGC endocervical favor neoplastic) hatten 9,4% (447) bzw. 2,2% (107), einen IIID1 (LSIL) 19% (906), einen IIID2 (HSIL, moderate Dysplasia) 18,9% (898), einen IVa-p (HSIL, severe Dysplasia) 10,7% (508), einen IVa-g (AIS) 0,7% (31), einen IVb-p (HSIL with Features suspicious for Invasion) bzw. IVb-g (AIS with Features suspicious for Invasion) 0,3% (15), 0,1% (6) und 7 v.a. auf Invasion V-p (squamous Cell Carcinoma)/V-g (endocervical Adenocarcinoma) (0,1%). In der Gruppe der IVa-p (HSIL, severe Dysplasia) ergab sich bei 67,7% eine CIN 2+ bzw. bei 56,5% eine CIN 3+, Adenocarcinoma in situ (AIS) und Adenokarzinom. Wertete man zusätzlich die Histologien der direkt aufgrund des kolposkopischen Befundes Exzidierten mit aus, ergab sich in 79,7% eine CIN 2+ bzw. 67,3% eine CIN 3+. Bei IIID2 (HSIL, moderate Dysplasia) ergab sich in 50,9% eine CIN 2+ bzw. bei 28,3% CIN 3+/AIS, dies erhöhte sich nach Auswertung der direkt Operierten auf 53,0% CIN 2+ bzw. auf 29,3% CIN 3+/AIS. Bei IIID1 (LSIL) zeigte sich in 27,4% eine CIN 2+ bzw. in 11,7% eine CIN 3+/AIS und bei II-p (ASC-US) bei 23,4% eine CIN 2+ bzw. 10,8% eine CIN 3+ und AIS und bei II-g (AGC endocervical NOS) in 34,4% eine CIN 2+ bzw. in 23,4% eine CIN 3+. In der Gruppe der HPV-Persistenz/II-a und I zeigte sich in 21% eine CIN 2+ bzw. in 12,1% eine CIN 3+ und AIS bzw. in 13% eine CIN 2+

und in 5,9% eine CIN 3+ und AIS. Bei den Patientinnen, die HPV-negativ waren und alleine aufgrund des zytologischen Abstrichs abgeklärt wurden, ergab sich in 27,9% eine CIN 2+ bzw. in 14,1% eine CIN 3 und AIS.

Diskussion

In Zusammenschau der vorliegenden Befunde unserer ersten Daten der Registerstudie zum neuen Zervixkarzinom-Screening, entsprechend der organisierten Krebsfrüherken-

nungs-Richtlinie (oKFE-RL), konnten wir zeigen, dass bei einem nicht unerheblichen Anteil, besonders in der zytologischen Niedrigrisikogruppe, die Zielläsion einer CIN 3+ und AIS unerwartet häufig nachgewiesen wird. Wir können heute nicht beantworten, ob sich dadurch die Inzidenz und die Mortalität des Zervixkarzinoms senken lässt, aber dies könnte ein erster Hinweis darauf sein und wird in weiteren Langzeitauswertungen überprüft.

Introduction

For the first time since women began receiving annual cancer screening examinations in 1971, new regulations for cervical cancer screening were introduced starting 1 January 2020. In November 2018, the Joint Federal Committee (G-BA) adopted a new guideline for cervical carcinoma screening [1, 2]. The annual gynecological screening examination remains in place. An organized cancer screening guideline (oKFE-RL) now applies to cervical carcinoma screening. This means that women from the age of 20 are invited by the statutory health insurance companies to have a check-up every five years until they reach the age of 65. In addition, a cytological smear is taken once a year from the age of 20. The cytological findings are determined according to the criteria of the Munich Nomenclature III (2014) [3]. From the age of 35, so-called co-testing is performed every three years. This means that in addition to the cytological smear, a test for the most common high-risk human papillomavirus (HPV) types is also performed. If abnormal smears are obtained during the screening, the following diagnostic algorithm applies:

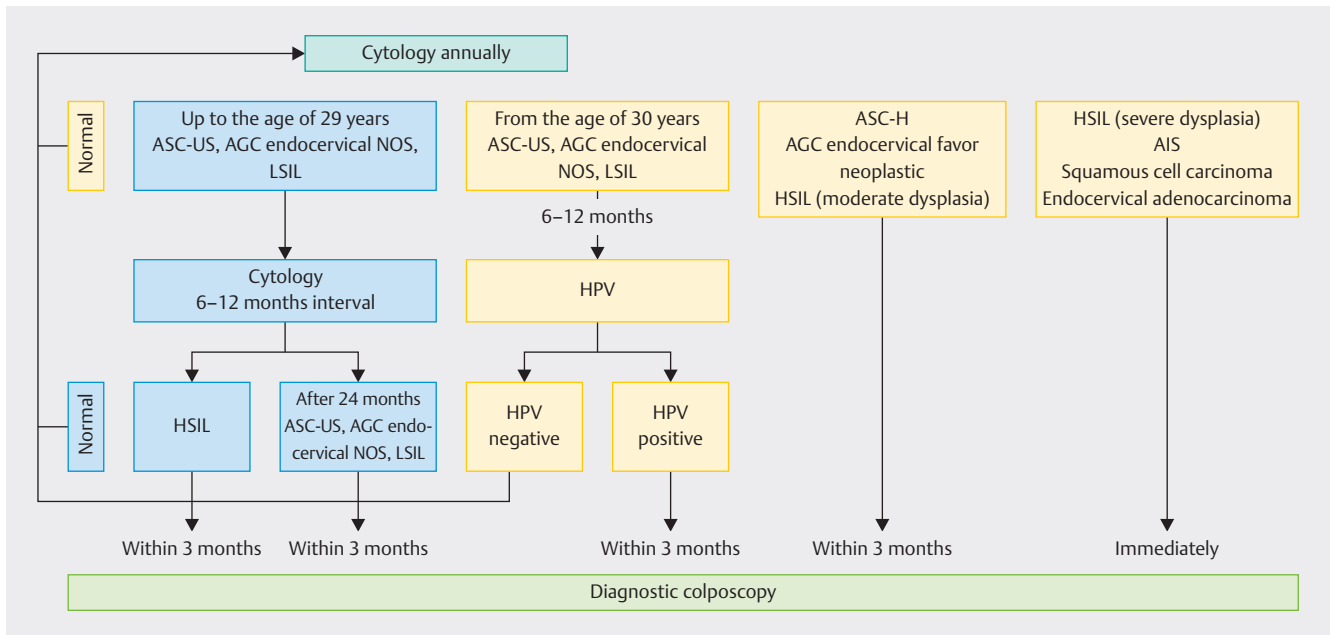
The diagnostic algorithm is shown in ► **Fig. 1** and ► **Fig. 2**. For women aged 20 to 34, annual cytological prevention screening continues to apply. However, they are divided into two age groups: 20 to 29 years and 30 to 34 years. The rationale for this subdivision is that young women have a high HPV prevalence with an overall low carcinoma risk. The likelihood of regression of these changes is high and therefore a diagnostic colposcopy is indicated only if these low-risk findings persist for more than 24 months. In the case of higher-grade cell changes, a diagnostic colposcopy should be performed within three months or immediately in the case of groups IV and V. For low-risk cytologic findings from 30 years of age, HPV testing should be performed after 6–12 months. Colposcopic diagnostic confirmation is then performed within three months if the HPV test is positive. If the HPV test is negative, the woman returns to annual screening.

For women from 35 years of age, the diagnostic algorithm is based on the findings from the co-test. If cytological group I, II-p (ASC-US), II-g (AGC endocervical NOS), and a negative HPV test are present, screening after three years is recommended. If group I/HPV is detected, retesting is recommended after 12 months. If both results are negative, the patient returns to primary screening. If cytological findings from group II-p (ASC-US), II-g (AGC endocervical NOS), or HPV persistence are detected, a diagnostic colposcopy should be performed within three months. The same proce-

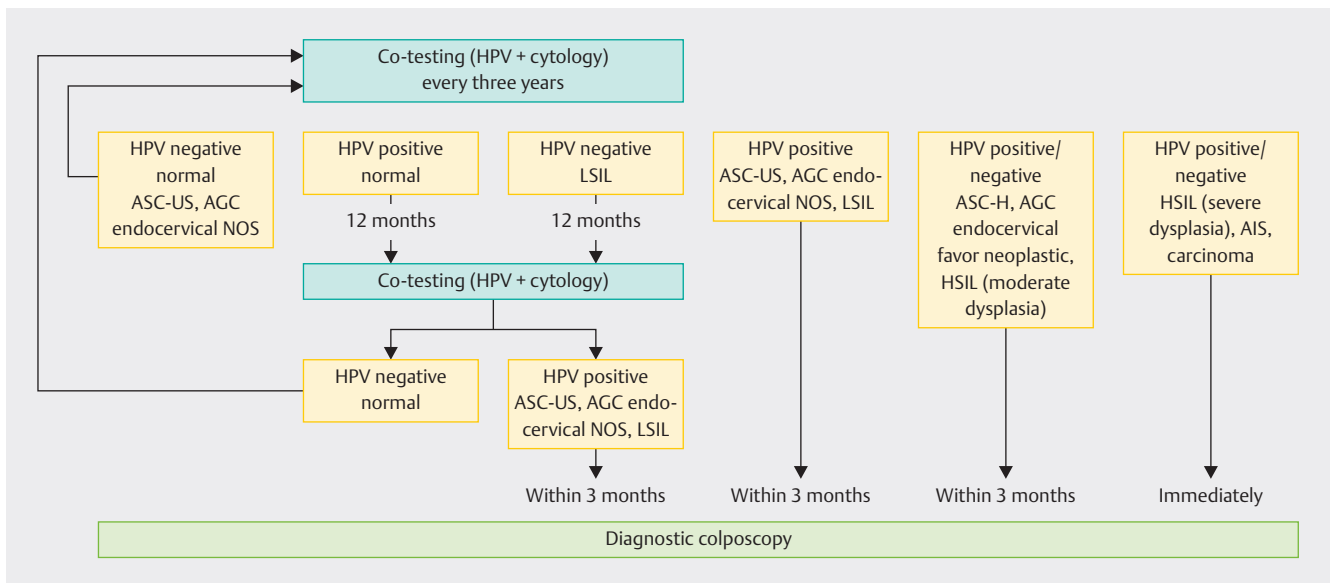
dures applies if the constellation group IIID1 (LSIL)/HPV-negative is present. Groups III-p (ASC-H), III-g (AGC endocervical favor neoplastic), IIID2 (HSIL, moderate dysplasia) regardless of the HPV test should be investigated colposcopically within three months. A colposcopy should be performed immediately for groups IV and V.

The cancer screening examination (KFU) has been established in Germany since 1971. According to the annual “Cervical Cytology” statistics, between 15 and 18 million women are examined each year as part of the KFU. A stable rate of about 1.6% of abnormal cytologies from group III (IIID1 [LSIL], IIID2 [HSIL, moderate dysplasia], III-p [ASC-H], g, IV, V) has been seen in recent years [4]. With regard to the diagnostic confirmation of these abnormal findings, certification of dysplasia consultations and dysplasia units accepted by the German Society of Gynecology and Obstetrics (DGGG), German Cancer Society (DKG), Working Group Oncology (AGO), and Working Group Cervical Pathology and Colposcopy (AG-CPC) has been in effect since 2014.

Since 1 January 2020, the diagnostic algorithm defined by the G-BA has been the basis for diagnostic confirmation of suspected cytological and virological findings. The diagnostic algorithm defines that the low-risk group of patients with high-risk HPV-positive cytologic findings of groups II-p (ASC-US), II-g (AGC endocervical NOS), and IIID1 (LSIL) should receive early colposcopic diagnostic confirmation. This approach has been strongly debated, especially considering the expected spontaneous remission rates and the low risk of progression in these patients. This approach appears to be justified only if there is evidence of high-risk HPV type 16/18 [5, 6, 7]. The resulting burden on the existing diagnostic capacities and the stress on the individual patients who do not have conclusive clarification of how urgent their diagnostic confirmation is, provides the basis for this multicenter cervical carcinoma registry study. As described above, the early collection of results is of utmost importance, especially in the low-risk group, as these are patients for whom the urgency is unclear and in whom overdiagnosis and potential treatment could cause great harm. This question is addressed in the present study with the collaboration of dysplasia units and consultations of the Working Group on Cervical Pathology and Colposcopy (AG-CPC) [8]. This paper presents and discusses the data collected during the diagnostic colposcopy. The focus is on the evaluation of the colposcopy as a diagnostic method. A diagnostic colposcopy is performed according to the specifications of the Rio nomenclature (IFCPC 2011) [9].



► **Fig. 1** Diagnostic algorithm according to G-BA 20–34 years (source: Association of German Cytology Assistants e.V. Cyto-Info 1/2020).



► **Fig. 2** Diagnostic algorithm according to G-BA from 35 years of age (source: Association of German Cytology Assistants e.V. Cyto-Info 1/2020).

Methods

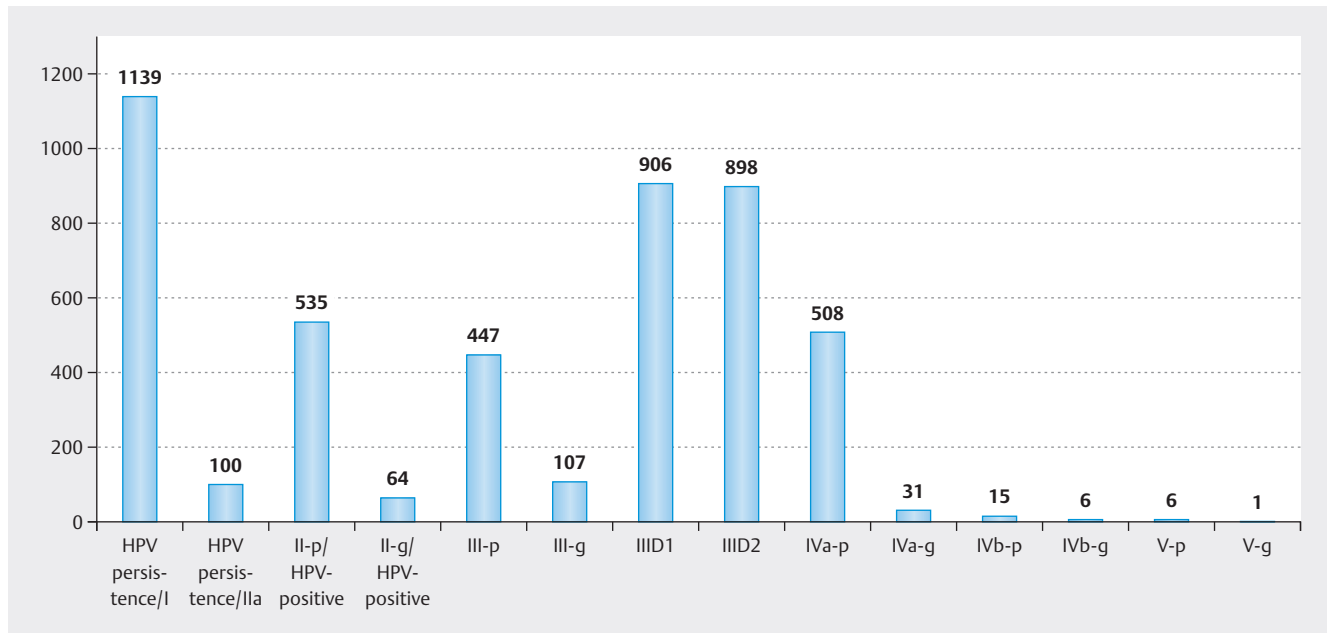
Patients and Data Collection

All patients who presented for a diagnostic colposcopy at the participating centers as part of the cervical carcinoma screening algorithm were informed about the study and enrolled after signing an informed consent form. The study was submitted to the Ethics Committee of the Medical Faculty of the Eberhard Karl University of Tübingen under project number 937/2019B02 and was approved in July 2020 (ClinTrials.gov number: DRKS-ID: DRKS00024931). Data on the following findings were collected:

Medical history, colposcopy, histology, and cytology findings, as well as possible therapies and their findings.

Participating centers

The following centers are taking part in the registry study: Dysplasia Unit of Park-Klinik Weißensee, Berlin; Dysplasia Unit of University Women's Hospital Dresden; Dysplasia Consultation PD Dr. Küppers, Düsseldorf; Dysplasia Unit of Helios Kliniken Erfurt, Dysplasia Consultation Unit of the University Women's Hospital Göttingen; Dysplasia Unit of amedes Medical Treatment Center for Gynecology, Munich; Dysplasia Consultation Unit of the Academic



► Fig. 3 Referral diagnoses at initial presentation.

Teaching Hospital of the University of Rostock; Dysplasia Consultation Unit Dr. J. Quaas, Stralsund, and the Dysplasia Unit of the University Women's Hospital Tübingen.

Statistics

The following evaluation presents the respective subgroups and their histological and colposcopic findings. Statistical analysis was performed using GraphPad Prism (version 9.5.0), Boston, Massachusetts, USA. Any comparisons drawn here were calculated using the χ^2 test. The significance level was $p = 0.05$.

Results

A total of 4763 patients were enrolled in the study from July 2020 to October 2022. Of these, 69.7% (3321) were from a university hospital/clinic and 30.3% (1442) were from a practice. On average, the patients were 41.0 years and IIG IP. Persistent nicotine abuse was reported by 29.5% of the participants, which is significantly higher compared to the data of the Federal Statistical Office for the female population with 15.7% ($p < 0.001$) (19).

Referral diagnosis

The reason for initial presentation was HPV persistence with cytologic group I in 23.9% (1139), HPV persistence with cytologic group II-a in 2.1% (100), II-p (ASC-US) in 11.2% (535), and II-g (AGC endocervical NOS) in 1.3% (64). III-p and III-g (AGC endocervical favor neoplastic) were present in 9.4% (447) and 2.2% (107), respectively, IIID1 (LSIL) in 19% (906), IIID2 (HSIL, moderate dysplasia) in 18.9% (898), IVa-p (HSIL, severe dysplasia) in 10.7% (508), IVa-g (AIS) in 0.7% (31), IVb-p (HSIL with features suspicious for invasion) and IVb-g (AIS with features suspicious for invasion) in 0.3% (15), 0.1% (6) and 7 patients presented with suspected invasion V-p (squamous cell carcinoma)/V-g (endocervical

adenocarcinoma) (0.1%), 6 of which with cytological group V-p (squamous cell carcinoma) and one with V-g (endocervical adenocarcinoma) (see ► Fig. 3).

HPV status

The proportion of HPV-positive patients was dominant among the women we presented in the diagnostic consultation. 4145 were high-risk HPV-positive (87%), 369 were HPV-negative (7.7%), and the HPV status was unknown in 249 patients (5.2%).

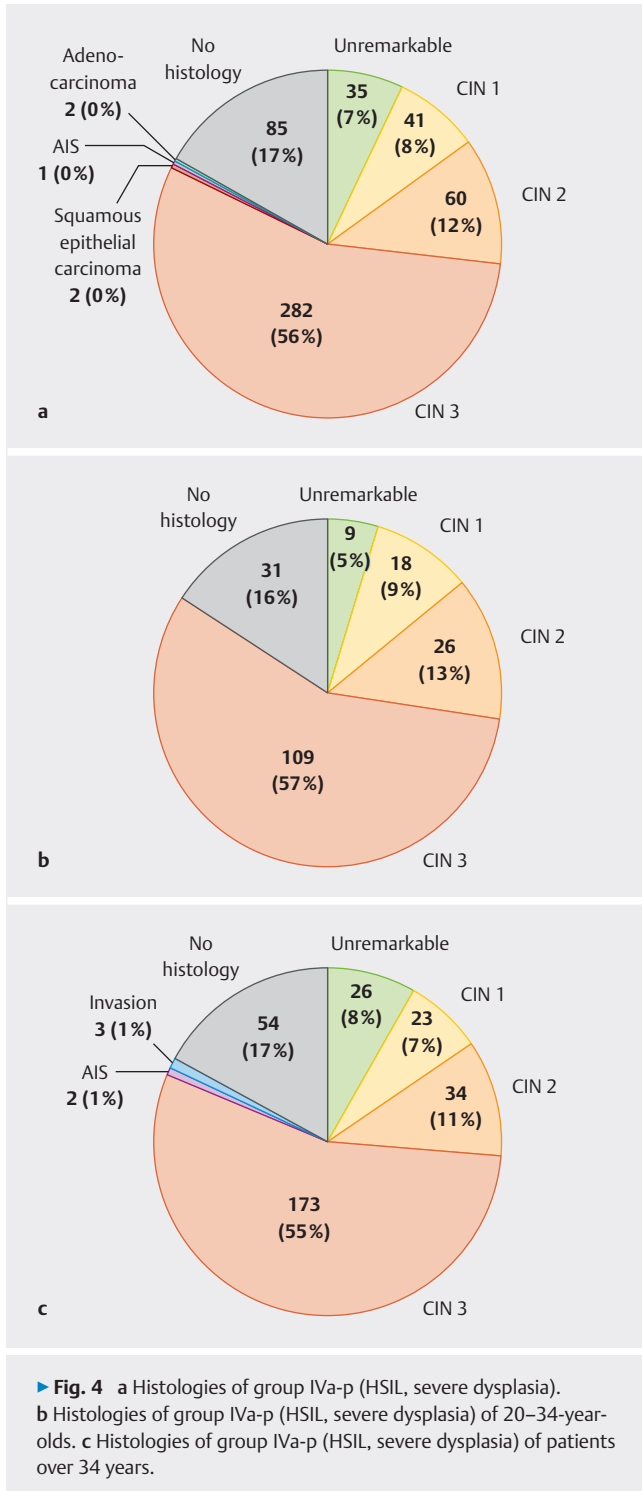
Group IVa-p (severe dysplasia – HSIL)

The data collected from the 508 patients (10.7%) patients with cytological group IVa-p (HSIL, severe dysplasia) are described below.

Colposcopically, major changes were most common (79.8%, 403), followed by minor changes (10.5%, 53). Physiological findings were obtained in 7.5% (38) and 2.0% (10) showed nonspecific abnormal findings. Suspected invasion was present in one patient. Only 0.6% (3) of patients could not be adequately assessed.

Histologically, the following findings were identified in this group: 8.1% (41) had CIN 1, 11.8% (60) had CIN 2, 55.5% (282) had CIN 3, and 0.4% (2) had squamous cell carcinoma (FIGO Ia2, FIGO Ib1). Histologically, adenocarcinoma in situ (AIS) was diagnosed in 0.4% (2), and adenocarcinoma (FIGO Ia2) was diagnosed in one patient (0.2%). Histology was unremarkable in 6.9% (35) and no histology was collected in 16.7% (85) (see ► Fig. 4a). This results in CIN 2+ in 67.7% of cases, and CIN 3+, AIS, and adenocarcinoma in 56.5% of cases, respectively.

Furthermore, the 16.7% of patients who did not receive a histological analysis by biopsy but underwent excision immediately based on their colposcopy findings were further examined. The histology of the excision was evaluated. This revealed CIN 3 in 84.1% (58), CIN 2 in 4.3% (3), CIN 1 in 2.9% (2), and unremarkable findings in 3.3% (3).



Thus, in this cytological group IVa-p, CIN 3 could be detected in 340 (66.9%) and CIN 2 in 62 (12.2%), as well as a squamous cell carcinoma (HSIL, severe dysplasia) in two cases, resulting in histological CIN 2+ in 79.7% and CIN 3+ in 67.3%, respectively.

If the patients are divided up into the two age groups according to the algorithm, the following findings are obtained:

In the group of 20–34-year-olds, 9.3% (18) showed CIN 1, 13.5% (26) showed CIN 2, and 56.5% (109) showed CIN 3. Histology was

unremarkable in 4.7% of cases (9) and no histology was collected in 16.1% of cases (31) (see ► Fig. 4b). Thus, 69.9% had CIN 2+, and 56.5% had CIN 3+.

In the group of patients over 34, 7.3% (23) had CIN 1, 10.8% (34) had CIN 2, 54.9% (173) had CIN 3, and 0.6% (2) had squamous cell carcinoma (FIGO Ia2, FIGO Ib1). Histologically, adenocarcinoma in situ (AIS) was diagnosed in 0.6% (2), and adenocarcinoma (FIGO Ia2) was diagnosed in one patient (0.3%). Histology was unremarkable in 8.3% (26), and no histology was collected in 17.1% (54) (see ► Fig. 4c). Thus, 67.3% had CIN 2+/AIS and 56.5% had CIN 3+/AIS.

Group IIID2 (moderate dysplasia – HSIL)

18.9% (898) of patients who presented as part of the diagnostic algorithm had a referral diagnosis of cytology group IIID2 (HSIL, moderate dysplasia).

Colposcopically, major changes were most common (46.5%, 416), followed by minor changes (40.6%, 363). Physiological findings were obtained in 10.3% (92), 1.8% (16) had nonspecific abnormal findings, and 0.9% (8) had other findings. Suspected invasion was not present in any of the patients. Only 0.3% (3) of patients could not be adequately assessed.

Histologically, this cytological group IIID2 (HSIL, moderate dysplasia) showed the following findings: 21% (189) had CIN 1, 22.7% (204) had CIN 2, and 28.2% (253) had CIN 3. Adenocarcinoma in situ (AIS) was diagnosed histologically in 0.3% (3). Histology was unremarkable in 21% (188) and no histology was collected in 6.8% (61) (see ► Fig. 5a). Thus, 50.9% had CIN 2+ and 28.3% had CIN 3+/AIS.

If the histology of the excision is evaluated in the 61 (6.8%) patients who did not receive histology but received excision immediately based on their colposcopy findings (n = 20), the overall result in this group was CIN 2+/AIS in 53.0%. Of these, one patient had CIN 1, nine had CIN 2, and ten had CIN 3. This results in CIN 3+/AIS in 29.3% of cases.

If the patients are also divided up here into the two age groups according to the algorithm, the following findings are obtained:

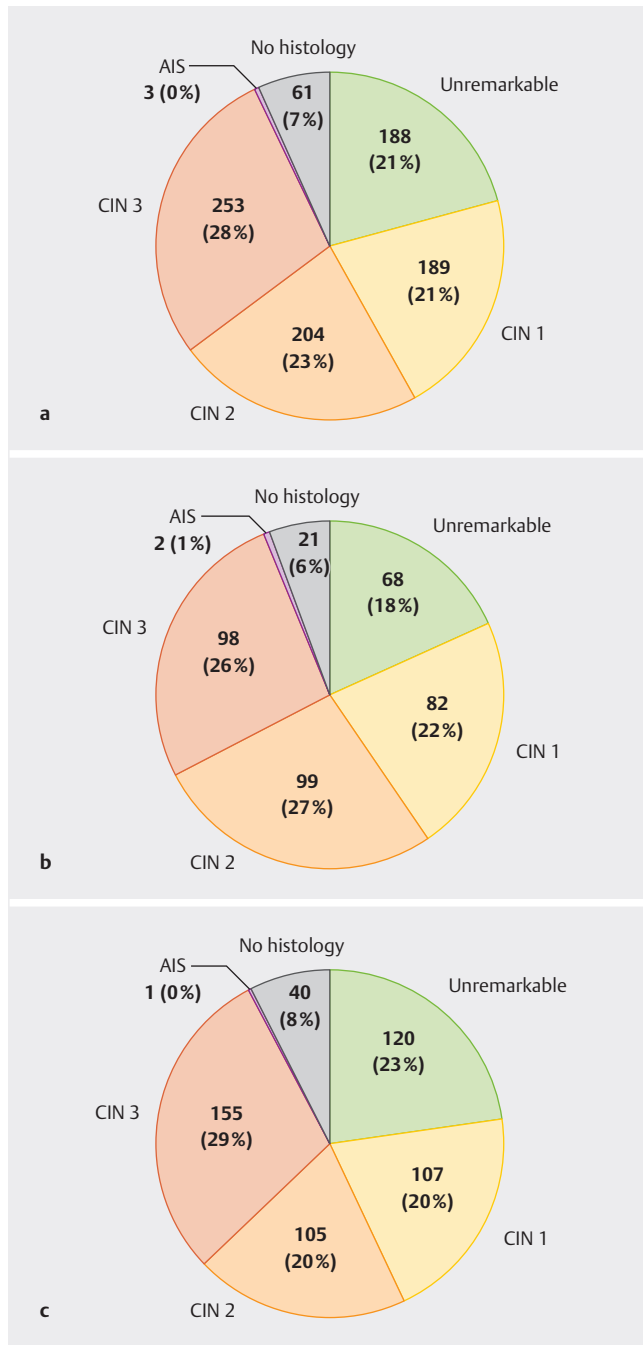
In the group of 20–34-year-olds, 22.2% (82) had CIN 1, 26.8% (99) had CIN 2, 26.5% (98) had CIN 3, and 0.5% (2) had AIS. Histology was unremarkable in 18.4% (68) and no histology was collected in 5.7% (21) (see ► Fig. 5b). Thus, 53.8% had CIN 2+ and 27% had CIN 3+.

In the group of patients over 34, 20.3% (107) had CIN 1, 19.9% (105) had CIN 2, and 29.4% (155) had CIN 3. Adenocarcinoma in situ (AIS) was diagnosed in one case. Histology was unremarkable in 22.7% (120) and no histology was collected in 7.6% (40) (see ► Fig. 5c). Thus, 49.4% had CIN 2+/AIS and 29.5% had CIN 3+/AIS.

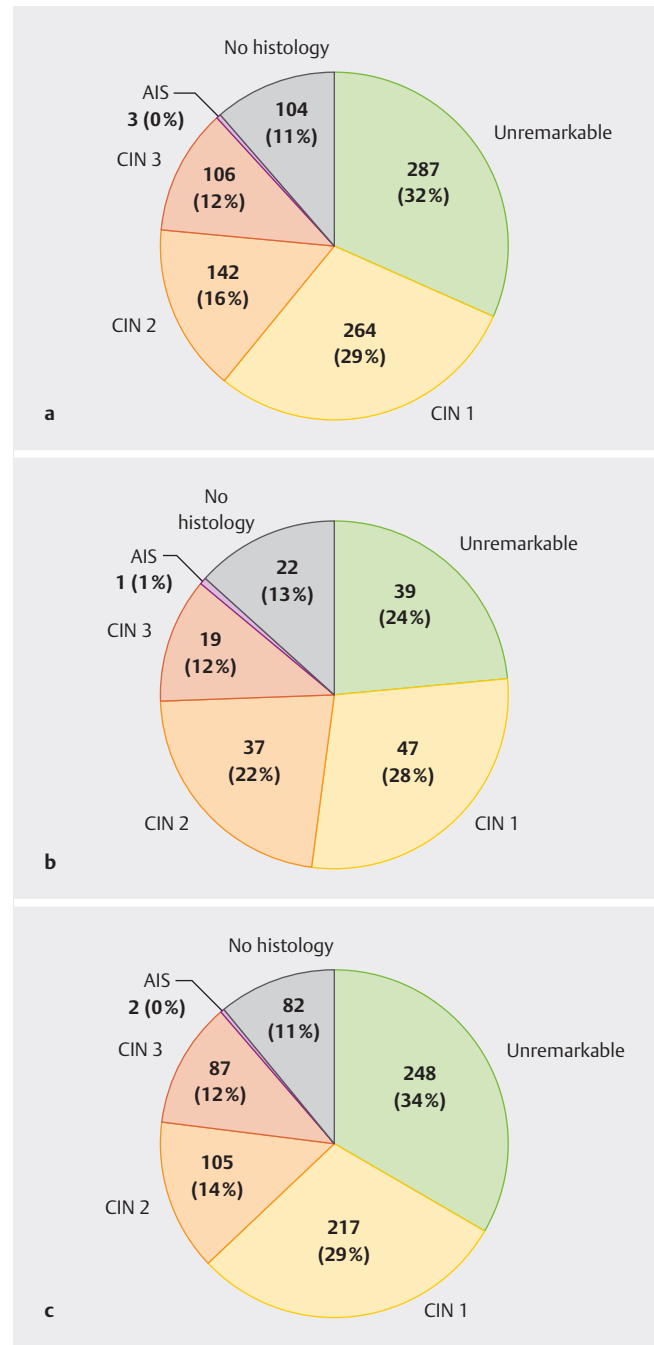
Group IIID1 (LSIL)

Each of the so-called low-risk groups are evaluated below, starting with cytological group IIID1 (LSIL), which consisted of 906 women.

Colposcopically, cytological group IIID1 (LSIL) showed minor changes most frequently (62.4%, 560), followed by major changes (18.3%, 164), and physiological findings were obtained in 15.6% (140). Nonspecific abnormal findings were seen in 3.2% (29) and other findings in 0.4% (4). Suspected invasion was not present in



► **Fig. 5** a Histologies of group IIID2 (HSIL, moderate dysplasia). b Histologies of group IIID2 (HSIL, moderate dysplasia) of 20–34-year-olds. c Histologies of group IIID2 (HSIL, moderate dysplasia) of patients over 34.



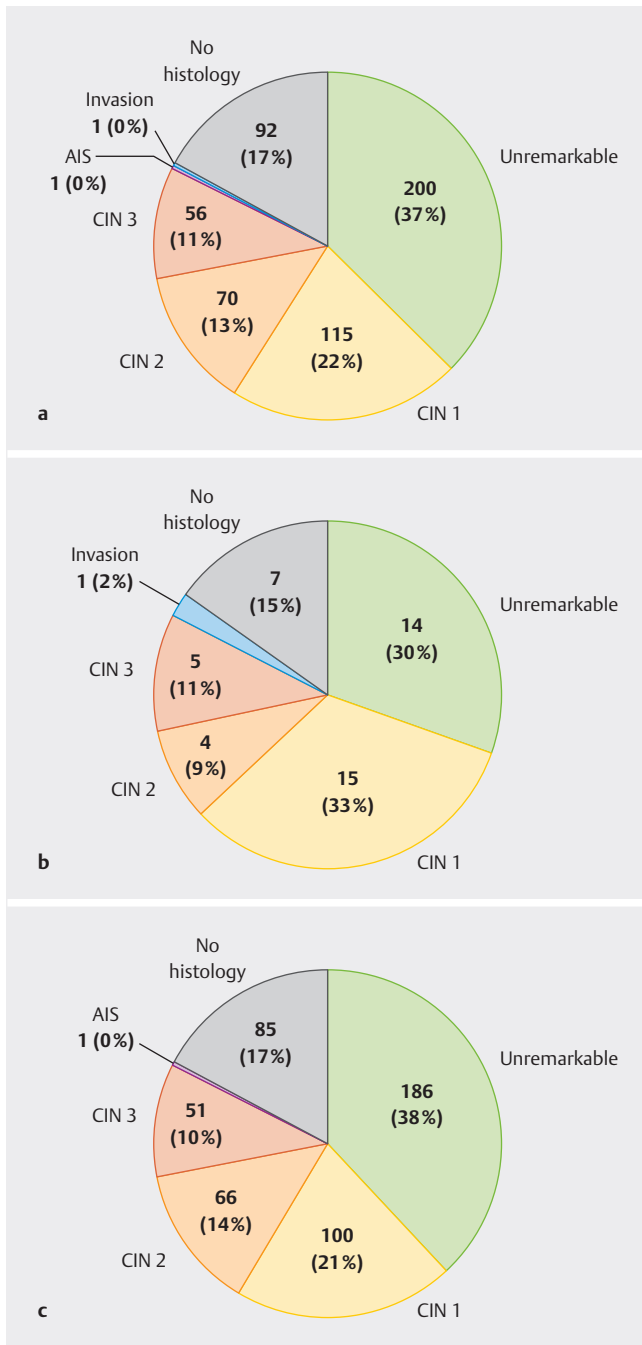
► **Fig. 6** a Histologies of group IIID1 (LSIL). b Histologies of group IIID1 (LSIL) of 20–34-year-olds. c Histologies of group IIID1 (LSIL) of patients over 34 years of age.

any of the patients. 1.0% (9) of patients could not be adequately assessed.

Of the 906 patients who presented with IIID1 (LSIL), CIN 1 was found in 29.1% (264), CIN 2 in 15.7% (142), and CIN 3 in 11.7% (106). Histology was unremarkable in 31.7% (287) and no histology was collected in 11.5% (104). AIS occurred in 3 cases (0.3%) (see ► **Fig. 6a**). Thus, in this cytologic group, CIN 2+ was present in 27.4%, and CIN 3+/AIS in 11.7%.

If the patients are also divided up here into the two age groups according to the algorithm, the following findings are obtained:

In the group of 20–34-year-olds, 28.5% (47) had CIN 1, 22.4% (37) CIN 2, 11.5% (19) CIN 3, and 0.6% (1) AIS. Histology was unremarkable in 23.6% (39) and no histology was collected in 13.3% (22) (see ► **Fig. 6b**). Thus, 34.5% had CIN 2+/AIS and 12.1% had CIN 3+/AIS.



► **Fig. 7** a Histologies of group II-p. b Histologies of group II-p of 20–34-year-olds. c Histologies of group II-p patients over 34 years.

In the group of patients over 34, 29.3% (217) had CIN 1, 14.2% (105) had CIN 2, and 11.7% (87) had CIN 3. Adenocarcinoma in situ (AIS) was diagnosed in two cases. Histology was unremarkable in 33.5% of cases (248) and no histology was collected in 11.1% of cases (82) (► **Fig. 6c**). Thus, 26.2% had CIN 2+/AIS and 12% had CIN 3+/AIS.

Group II-p (ASC-US)

In the group of participants presenting with cytology group II-p (535), colposcopically minor changes were most frequent (54.8%,

291), followed by physiological changes with 26.6% (141). Major changes were detected in 13.6% (72) and nonspecific abnormal findings in 3.8% (20). Other findings were found in 1.3% of cases (7). Suspected invasion was not present in any of the patients. 0.7% (4) of patients could not be adequately assessed.

Histologically, this cytological group II-p showed the following findings: 21.5% (115) CIN 1, 13.1% (70) CIN 2, 10.5% (56) CIN 3. One patient (0.2%) showed squamous cell carcinoma (FIGO Ia2) and 0.2% (1) showed AIS. Histology was unremarkable in 37.4% (200) and no histology was collected in 17.2% (92) (see ► **Fig. 7a**). Thus, 23.4% had CIN 2+ and 10.8% had CIN 3+ and AIS.

If the patients are also divided up here into the two age groups according to the algorithm, the following findings are obtained:

In the group of 20–34-year-olds (46), CIN 1 was present in 32.6% (15), CIN 2 in 8.7% (4), CIN 3 in 10.9% (5), and a carcinoma described above in one case. Histology was unremarkable in 30.4% (14) and no histology was collected in 15.2% (7) (see ► **Fig. 7b**). Thus, 23.8% had CIN 2+/AIS and 13% had CIN 3+/AIS.

In the group of patients over 34 (489), 20.4% (100) had CIN 1, 13.5% (66) had CIN 2, and 10.4% (51) had CIN 3. Adenocarcinoma in situ (AIS) was diagnosed in one case. Histology was unremarkable in 38% of cases (186) and no histology was collected in 17.4% of cases (85) (see ► **Fig. 7c**). Thus, 24.1% had CIN 2+/AIS and 10.6% had CIN 3+/AIS.

Group II-g (AGC endocervical NOS)

In the group of participants presenting with cytology group II-g (AGC endocervical NOS) (64), colposcopically minor changes were most frequent (48.4%, 31), followed by physiological changes with 26.6% (17). Major changes were seen in 21.9% (14) and other findings were seen in 3.1% (2). Suspected invasion and nonspecific abnormal findings were not present in any of the patients.

Histologically, this cytological group II-g (AGC endocervical NOS) showed the following findings: 20.3% (13) CIN 1, 10.9% (7) CIN 2, 23.4% (15) CIN 3. Histology was unremarkable in 40.6% (26) and no histological analysis was performed in 4.7% (3) (see ► **Fig. 8**). This results in CIN 2+ in 34.4% and CIN 3+ in 23.4%. CIN 2+ is not found significantly more frequently in cytology group II-g (AGC endocervical NOS) (34.4%) compared to group II-p (23.4%) ($p = 0.0676$).

A distinction between age groups was not made in only five patients under 35 years of age.

HPV persistence/II-a (NILM)

Furthermore, 99 patients with cytological group II-a and HPV persistence were evaluated. Here, colposcopic findings were most frequently physiological (38%, 38), followed by minor changes with 35% (35). Major changes were detected in 23% (23), nonspecific abnormal findings in 3% (3), and other findings in one patient.

Histologically, this cytological group II-a/HPV persistence showed the following findings: 13% (13) CIN 1, 10% (10) CIN 2, and 11% (11) CIN 3. In one case, the histology of the biopsy revealed an AIS. Histology was unremarkable in 58% (58) and no histological analysis was performed in 7% (7) (see ► **Fig. 9**). In this group, CIN 2+ occurs in 21% of cases, and CIN 3+ and AIS occurs in 12.1% of cases.

A distinction between the age groups was also not made here in only 14 female patients under 35 years of age.

HPV persistence/I (NILM)

In the largest group of patients (1139) presenting with cytological group I and HPV persistence, the most common colposcopic findings were physiological (48%, 541), followed by minor changes at 32.5% (367). Major changes were detected in 8.4% (95), non-specific abnormal findings in 8% (90), and other findings in 3.1% (35). 1% (11) of patients could not be adequately assessed.

Histologically, this cytological group I/HPV persistence showed the following findings: 17.5% (199) CIN 1, 7.3% (83) CIN 2, 5.6% (64) CIN 3. In one case, the histology of the biopsy revealed squamous cell carcinoma FIGO stage Ia2. AIS was seen in 0.2% (2), unremarkable histology in 43.6% (497), and no tissue sample was obtained in 25.7% (293) (see ► Fig. 10). Thus, in this group, CIN 2+ was present in 13% and CIN 3+ and AIS in 5.9%.

When the different age groups were considered, it was found that only 25 patients in this group were younger than 35 years of age. Therefore, an age-based subgroup examination was not performed in this group.

HPV-negative

Finally, we report on the 369 patients who tested HPV-negative and presented for diagnostic colposcopy based solely on their cytological findings.

Here, 2.2% (8) patients had II-p (ASC-US), 21.1% (78) had III-p (ASC-H), 11.1% (41) had III-g (AGC endocervical favor neoplastic), 11.1% (41) had IIID1 (LSIL), 38.8% (143) had IIID2 (HSIL, moderate dysplasia), and 13.8% (51) had IVa-p (HSIL, severe dysplasia). Only four presented with IVa-g (AIS), one with IVb-p (HSIL with features suspicious for invasion), and two with IVb-g (AIS with features suspicious for invasion) (see ► Fig. 11).

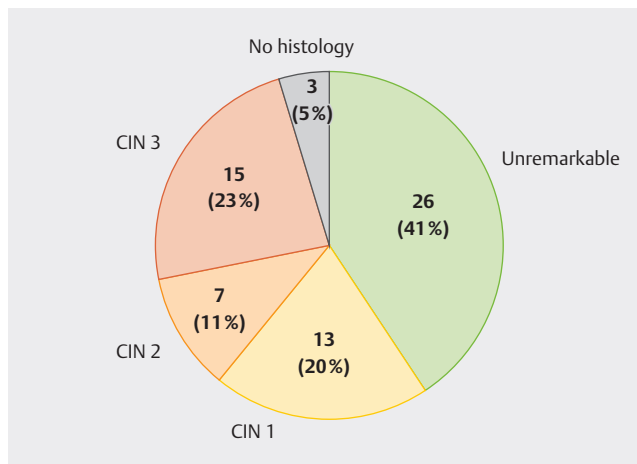
Among patients who were HPV-negative, colposcopically minor changes were most common with 36.6% (134), followed by major changes (34.4%, 126). Physiological findings were obtained in 22.4% (82), nonspecific abnormal findings in 4.1% (15), and other findings in 2.5% (9). 0.8% (3) of patients could not be adequately assessed.

Histologically, the following findings were seen in this group who presented with HPV-negative findings: 24.7% (91) had CIN 1, 14.1% (52) had CIN 2, 13.8% (51) had CIN 3. Histology revealed AIS in 0.3% (1). Histology was unremarkable in 31.5% (116) and no histology was collected in 15.7% (58) (see ► Fig. 12a). In this group, CIN 2+ was present in 27.9% and CIN 3 and AIS in 14.1%.

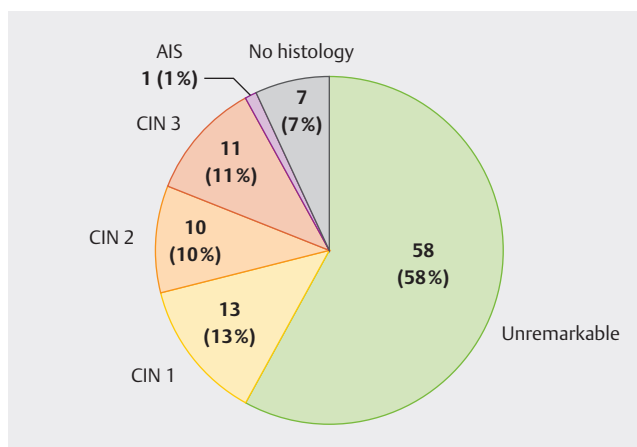
If the patients are also divided up here into the two age groups according to the algorithm, the following findings are obtained:

In the group of 20–34-year-olds (120), 20% (24) had CIN 1, 20.8% (25) had CIN 2, 24.2% (29) had CIN 3, 17.5% (21) had unremarkable histology, and no histology was collected in 17.5% (21) (see ► Fig. 12b). Thus, 45% had CIN 2+ and 24.2% had CIN 3+.

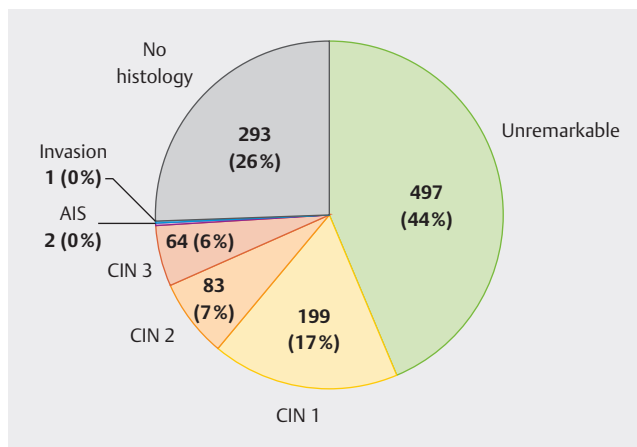
In the group of patients over 34 (249), 26.9% (67) had CIN 1, 10.8% (27) had CIN 2, and 8.8% (22) had CIN 3. AIS was diagnosed in one case. Histology was unremarkable in 38.2% (95) and no histology was collected in 14.9% (37) (see ► Fig. 12c). Thus, 20.1% had CIN 2+/AIS and 9.2% had CIN 3+/AIS.



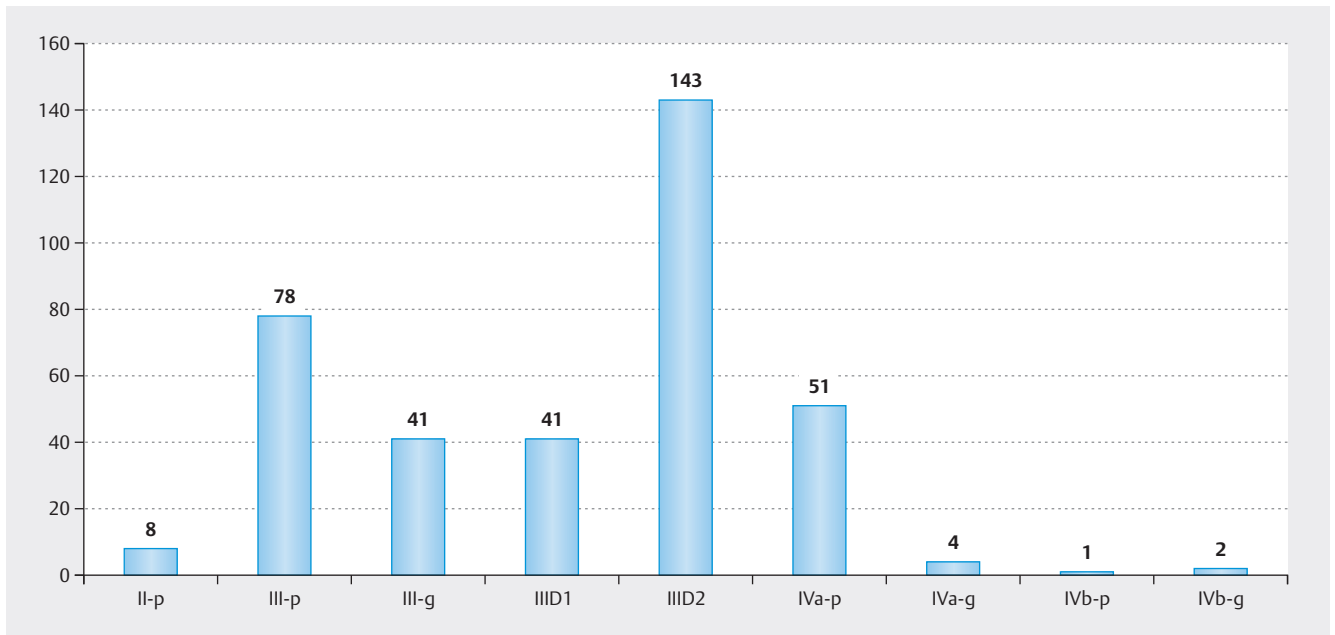
► Fig. 8 Group II-g histologies (AGC endocervical NOS).



► Fig. 9 Histologies of the HPV persistence/II-a group.



► Fig. 10 Histologies of the HPV persistence/I group.



► Fig. 11 Cytologies in HPV negativity.

Discussion

The new organized cancer screening guideline (oKFE-RL) for cervical cancer screening, which was introduced in Germany in January 2020, regulates in detail the procedures of diagnostic confirmation in the event of abnormal findings [1, 2]. This includes, firstly, that women over the age of 20 receive an invitation letter from the statutory health insurers. The importance of this invitation letter is reflected in the fact that, as Marquardt et al. have shown, the main cause for the development of cervical carcinoma in Germany is not attending the screening [10]. Furthermore, diagnostic confirmation centers around the colposcopy, which is performed in certified dysplasia consultations and units. In addition to the diagnostic confirmation procedures to be carried out, the legislature stipulates consistent documentation. This is to be evaluated at a later stage – after 2026 – by the Leipzig Registry Office. Since it was foreseeable that these documentation procedures could not be organized in the first year of the new screening, the AG-CPC initiated the registry study in June 2020. By October 2022, 4763 patients had already undergone colposcopic examinations at the nine participating consultations. A quarter of these patients had HPV persistence with unremarkable cytology. If the patients with abnormal cytology are also taken into account, the rate of HPV positivity rises to 87%. This high proportion can be explained by the preselection based on the new clarification algorithm. Overall, available data from Xhaja et al. show that in primary screening starting at age 35, 6.41% of cytologically healthy women were high-risk HPV-positive during co-testing; Marquardt et al. report 5.82% [11, 12]. These different positivity rates for high-risk HPV depend on regional differences, but also on the method used to perform the HPV test.

Knowing that, until 2019, women presented in the dysplasia consultations and units predominantly with suspicious cytology,

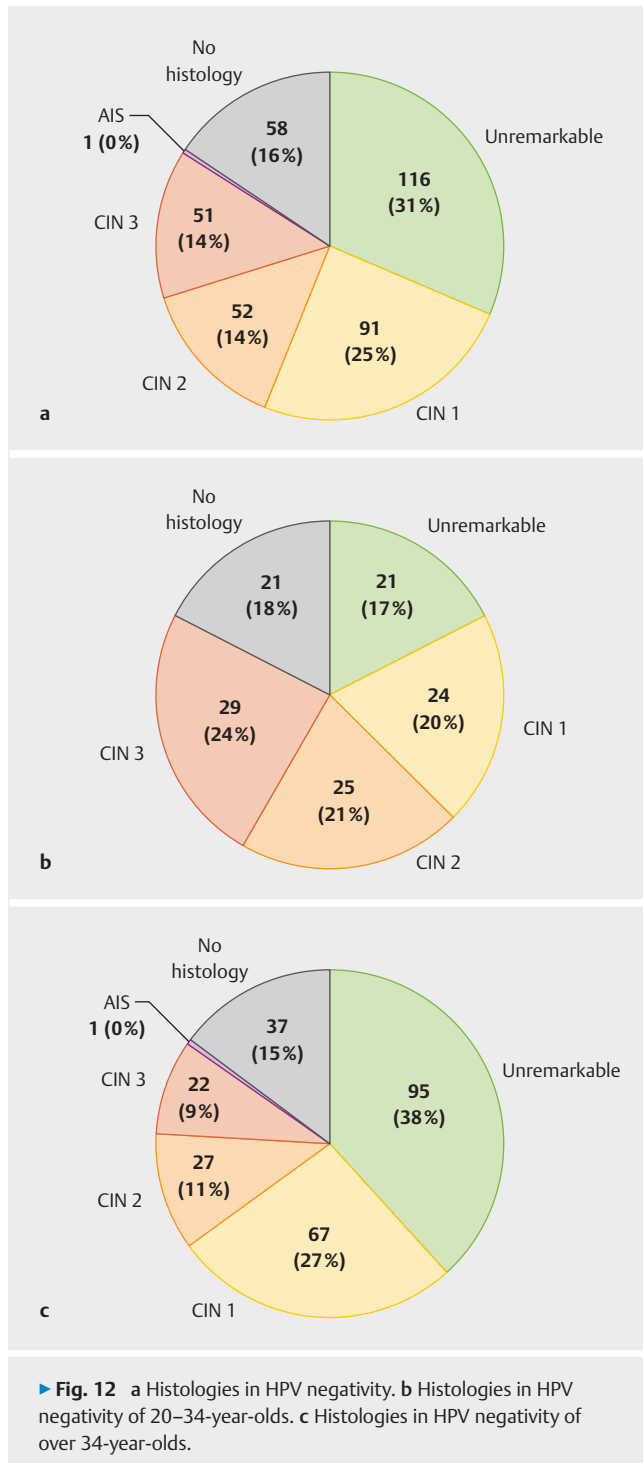
regardless of HPV status, the positivity rates for HPV above explain the increased strain on these consultation hours. If HPV persistence is detected and checked after 12 months, diagnostic colposcopy is indicated within three months. The diagnostic algorithm was followed for all patients enrolled here.

The target lesions for diagnostic consultations in the new screening are CIN 3+ lesion, AIS, and adenocarcinoma of the cervix. These findings are treated depending on the stage. Individual rules apply almost exclusively in pregnancy, and surgical diagnostic confirmation is rare in this phase of life. Outside of pregnancy, interventional treatment is usually performed, since, depending on the literature, progression of CIN 3 to cervical carcinoma can be expected to be up to 12% [13, 14, 15, 16, 17, 18].

All patients were asked about their nicotine abuse. 29.5% of participants reported nicotine abuse, which is significantly higher compared to the data from the Federal Statistical Office [19]. This suggests that nicotine abuse, among other factors, is a risk factor in the genesis of cervical carcinoma and its precursors, in addition to HPV infection. We did not ask about other co-morbidities in the survey questionnaires.

We would also have liked to address the importance of identifying the subtype of high-risk HPV. But experience from the various dysplasia consultations and units shows that when patients present to these specialty consultations, data transfer on HPV testing is incomplete. Not only is information on the HPV testing system missing. Information about which HPV type was detected is often also not specified: HPV type 16, HPV type 18, or the other HPV types (“others”). In addition, the HPV testing systems used in routine clinical practice are not comparable in terms of subtype determination. Therefore, we cannot make a statement in this study regarding the risk profile of the different HPV subtypes.

The other data collected will be discussed in relation to the cytological group of findings and HPV findings. Here, the correlation



between the cytological result and the HPV test result, collected outside the dysplasia consultation, is evaluated and interpreted with the colposcopic findings. Special consideration is given to the histological results after taking a biopsy of the cervix.

In the cytological group IVa-p (HSIL, severe dysplasia) we find colposcopically “major changes” in 79.8%. Regardless of the colposcopy findings, CIN 2+ lesions are detected in 79.7% of cases in this group. This high proportion can be explained by the patients biopsied primarily in the diagnostic colposcopy and the final histol-

ogy in the patients who were operated on immediately without preoperative histological confirmation of the diagnosis. Squamous cell carcinoma (early tumor stage) was detected twice. When comparing the CIN 3+ rate of 67.3% with the data from Marquardt et al. [12], which reported a CIN 3+ rate of 74.5% in group IVa-p (HSIL, severe dysplasia), our figures are lower. One explanation for this lower rate could be that in the study by Marquardt et al. data were only collected from one laboratory. In our registry study, cytological results from numerous different cytology laboratories were used as indications for further procedures and were not centrally controlled in one laboratory before colposcopic examination. Thus, no uniform evaluation standards can be applied here. The colposcopy findings obtained, especially the percentage of major changes, correspond to the histological results.

Considering the cytological group IIID2 (HSIL, moderate dysplasia), CIN 2+ is present in 50.9% of cases; after excision therapy, this rate increases minimally to 53%. This corresponds with the colposcopic rate of 46.5% “major changes” and 1.8% nonspecific abnormal findings. Again, if we consider our target lesion CIN 3+, this was seen in 29.2%; this correlates very well with the results of Marquardt et al. 2022, who diagnosed CIN 3+ in 31% of patients in group IIID2 (HSIL, moderate dysplasia). If we look at the numbers from the 2015 annual statistics of cytology laboratories in Germany [4], we find less CIN 3+ in PAP IIID2 (HSIL, moderate dysplasia) in the new screening than in 2015 annual cytology screening. Here, among the women in whom histology was performed and with a group IIID2 (HSIL, moderate dysplasia), CIN 3 or AIS were histologically detected in 40.1%. This should not be interpreted as a failure of the new screening. Rather, we are now seeing patients with a group IIID2 (HSIL, moderate dysplasia) earlier than ever in the histological analysis. Cumulatively, however, the rate of CIN 3+ and AIS will increase the longer the IIID2 (HSIL, moderate dysplasia) findings persist and the later the histological analysis is performed. The approach in the old screening until 2019 was to clarify the persistent findings, at the earliest after one year. The new screening has the concept of detecting patients with CIN 3/AIS in group IIID2 (HSIL, moderate dysplasia) as early as possible. Whether the current screening situation will decrease the incidence of cervical carcinoma is not currently foreseeable.

The following discusses the findings obtained in patients with low-risk cytologic groups II-p (ASC-US), II-g (AGC endocervical NOS), and IIID1 (LSIL). In group IIID1 (LSIL), as expected, colposcopically “minor changes” are shown most frequently with 62.4%. Histologically, however, CIN 2+ is found in 27.4% of cases in this cytological group. If we again consider our target lesion, this study showed CIN 3+ in 11.7% (AIS in 0.3%); Marquardt et al. (2022) reported 7.3%. Our detection rate of CIN 3+ is thus comparatively higher, but corresponds well with the colposcopic findings in this group of as many as 18.3% “major changes”. The main reason will be that the diagnostic confirmation rate in the registry study for this group of patients was higher than in the study by Marquardt et al. [12].

In group II-p (ASC-US), with a histological analysis rate of 82.8%, CIN 3+ was found in 10.7%. Surprisingly, AIS and squamous cell carcinoma were detected once each, respectively. If this is compared with the data from Marquardt et al. [12], which only diagnosed CIN 3+ in 1.4%, the figures in this registry study are sig-

nificantly higher. This can be explained in particular by the higher histological analysis rate in our study. Our histologically confirmed cases of CIN 2+ correspond to the number of colposcopic “major changes” detected. This discrepancy in the data may also reflect how variable the criteria for assigning group II-p (ASC-US) are in different cytology laboratories. In any case, in the cytology laboratories whose patients were included in the registry study, CIN 2+ lesions were concealed much more frequently behind group II-p (ASC-US) than in Marquardt et al. [12].

Cytological group II-g (AGC endocervical NOS) presents as a rather small group with only 64 patients, but it shows a relatively high rate of CIN 3+ with 23.4%. These high figures have not yet been recorded in any major study, not even in the 2015 annual statistics. One critical note with regard to the annual statistics of 2015 is that the diagnostic confirmation rate in this cytological findings group was very low at only 1.02%. Based on the data we have collected, there may need to be a revision of the classification of the low-risk cytological groups defined in Munich Nomenclature III. A comparison of our results for groups II-p (ASC-US) and II-g (AGC endocervical NOS) shows a statistical trend, but no significance with regard to CIN 2+.

In patients presenting with unremarkable cytology and HPV persistence, group I (NILM) and group II-a (NILM) were evaluated separately. It was suspected that group II-a (NILM)/HPV persistence has a higher risk of CIN 3+ lesion than group I. After all, group II-a (NILM) indicates a past medical history of morphological abnormalities of the cervix. As described in Munich Nomenclature III [3], group II-a (NILM) is indeed assigned in distinction to group I (NILM) when there is an abnormal medical history (cytological/histological/colposcopic/clinical findings). Our assumption was then confirmed. This is because the largest group we examined colposcopically, with cytological group I (NILM) and HPV persistence, shows CIN 3+ and AIS only half as often (at 5.9%) as group II-a (NILM) with HPV persistence (11% CIN 3, AIS). In both groups, the number of CIN 2+ corresponds to the “major changes”. Thus, we demonstrated that colposcopic major change findings were assigned three times more frequently in patients with group II-a (NILM) than in patients with group I (NILM). The rate of major changes in patients with group I (NILM) correlates with the data from Berger et al. (2023) [20]. However, in this small case study, no subgroup analysis was performed between groups I (NILM) and II-a (NILM), but all patients with normal cytological findings were evaluated together. However, interpretation of our results in patients with group II-a (NILM) is difficult because we do not have access to the medical history data of enrolled patients with this group of findings in the registry study. Thus, we do not know what prior diagnosis led to the assignment of group II-a (NILM). According to the G-BA decision, HPV persistence may be behind this group, as well as cytological, histological, colposcopic, or clinical previous findings. It is important to ensure that patients are assigned group II-a (NILM) according to uniform criteria.

In the low-risk cytologic groups and in the high-risk cytologic groups, we performed an age-based analysis of our data. Separate evaluations in women aged 20–34 years and 35 years and older showed no differences in CIN 2+ or CIN 3+ rates in these cohorts. In women with HPV persistence, such an age-dependent subgroup analysis was not performed because, as expected, in the group of

women aged 20–34 years, HPV persistence was checked only in very few cases. This is not even required according to the valid diagnostic algorithm. Surprisingly, some HPV examinations with negative test results were found in women aged 20–34 years and in women aged 35 years and older. Thus, an age-dependent subgroup study could be performed in this group.

The evaluation of HPV-negative patients who had an indication for a diagnostic colposcopy shows a relatively low proportion of CIN 2+ lesions (28.4%) independent of age; only 13.8% had CIN 3. The differences are astonishing when an age-dependent evaluation is performed. The rate of CIN 2+ and CIN 3 is more than twice as high in women aged 20–34 years compared with women aged 35 years and older. These results support the hypothesis that HPV diagnosis before the age of 35 years is not useful in screening. In addition, it should be noted that these data could only be collected because the young patients were incorrectly tested for HPV prior to presentation for a diagnostic colposcopy outside the guidelines of the oKFE-RL. These data suggest that deviating from the predetermined algorithm is not useful. A negative HPV test with a cytological examination that requires clarification must not result in a diagnostic colposcopy not being performed. The test result collected in this subgroup should not be confused with the false-negative rate for HPV assumed in primary HPV screening. It is well known that a false-negative rate of 4.5% is assumed for the first hybrid capture test 2 used in routine clinical practice for CIN 2 and CIN 3 [21]. More recent studies hypothesize a false-negative rate of almost 10% [22].

In a synopsis of the present findings of our initial data of the registry study on the new cervical cancer screening, according to the organized early cancer screening guideline (oKFE-RL), we can show that the target lesion CIN 3+ and AIS is detected unexpectedly frequently in a not insignificant proportion, especially in the cytological low-risk group. It is too early to draw a definitive summary. The available figures may suggest that in HPV persistence with abnormal group I cytology (NILM), a diagnostic colposcopy is indicated only after HPV persistence of 24 months; thus, HPV persistence confirmed in co-testing after 12 months initially has no further consequence, but co-testing must be repeated after another 12 months. This then leads to a diagnostic colposcopy in case of further HPV persistence. It can be assumed that this will reduce the number of unnecessary diagnostic colposcopies. However, based on the results of our study, we must explicitly state that women with normal cytology who have an abnormal medical history (group II-a, NILM) should receive a diagnostic colposcopy after 12 months of HPV persistence.

Today, we cannot answer whether the cervical carcinoma screening newly introduced in 2020 in accordance with the oKFE-RL can reduce the incidence and mortality of cervical carcinoma. We note that the new screening enables a very early diagnosis of CIN 3. This is possible because the diagnostic algorithm requires patients with abnormal findings to be sent for a diagnostic colposcopy at a very early stage. However, our data also indicate that due to the very early clarification diagnosis, a large number of young women with confirmed CIN 1 and CIN 2 are at risk of overtreatment. This is often superfluous, as remission can often be expected in this group, but progression occurs rarely [17, 23]. After all, even a recently published study showed that women under

25 years of age with CIN 3 have a regression rate of 29% and thus in individual cases even in these young women an initially conservative, prospective not immediately surgical procedure can be discussed [24]. In these young women and in those with CIN 1 and CIN 2 with an existing desire to have children, the harm would be great if the overtreatment increased the incidence of premature births [25]. It should be noted that especially in women < 30 years, the risk of preterm birth after conization seems to be high [26].

Clinical Trial

DRKS - Deutsches Register Klinischer Studien |
Registration number (trial ID): DRKS00024931

Conflict of Interest

The authors declare that they have no conflict of interest.

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