Thieme

Interdisciplinary Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer. Guideline (S3-Level, AWMF Registry Nummer 032/034-OL, April 2018) – Part 1 with Recommendations on the Epidemiology, Screening, Diagnosis and Hereditary Factors of Endometrial Cancer

Interdisziplinäre Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom. Leitlinie (S3-Level, AWMF-Register-Nummer 032/034-OL, April 2018) – Teil 1 mit Empfehlungen zur Epidemiologie, Früherkennung, Diagnostik und hereditären Faktoren des Endometriumkarzinoms

Authors

Günter Emons[1], Eric Steiner[2], Dirk Vordermark[3], Christoph Uleer[4], Nina Bock[1], Kerstin Paradies[5], Olaf Ortmann[6], Stefan Aretz[7], Peter Mallmann[8], Christian Kurzeder[9], Volker Hagen[10], Birgitt van Oorschot[11], Stefan Höcht[12], Petra Feyer[13], Gerlinde Egerer[14], Michael Friedrich[15], Wolfgang Cremer[16], Franz-Josef Prott[17], Lars-Christian Horn[18], Heinrich Prömpeler[19], Jan Langrehr[20], Steffen Leinung (†)[21], Matthias W. Beckmann[22], Rainer Kimmig[23], Anne Letsch[24], Michael Reinhardt[25], Bernd Alt-Epping[26], Ludwig Kiesel[27], Jan Menke[28], Marion Gebhardt[29], Verena Steinke-Lange[30], Nils Rahner[31], Werner Lichtenegger[32], Alain Zeimet[33], Volker Hanf[34], Joachim Weis[35], Michael Mueller[36], Ulla Henscher[37], Rita K. Schmutzler[38], Alfons Meindl[39], Felix Hilpert[40], Joan Elisabeth Panke[41], Vratislav Strnad[42], Christiane Niehues[43], Timm Dauelsberg[44], Peter Niehoff[45], Doris Mayr[46], Dieter Grab[47], Michael Kreißl[48], Ralf Witteler[27], Annemarie Schorsch[49], Alexander Mustea[50], Edgar Petru[51], Jutta Hübner[52], Anne Derke Rose[43], Edward Wight[53], Reina Tholen[54], Gerd J. Bauerschmitz[1], Markus Fleisch[55], Ingolf Juhasz-Boess[56], Lax Sigurd[57], Ingo Runnebaum[58], Clemens Tempfer[59], Monika J. Nothacker[60], Susanne Blödt[60], Markus Follmann[61], Thomas Langer[61], Heike Raatz[62], Simone Wesselmann[63], Saskia Erdogan[1]

Affiliations

1 Klinik für Gynäkologie und Geburtshilfe, Universitätsmedizin Göttingen, Göttingen, Germany
2 Frauenklinik, GPR Klinikum Rüsselsheim am Main, Rüsselsheim, Germany
3 Radiotherapy, Universität Halle/Saale, Halle/Saale, Germany
4 Facharzt für Frauenheilkunde und Geburtshilfe, Hildesheim, Hildesheim, Germany
5 Konferenz Onkologischer Kranken- und Kinderkrankenpflege, Hamburg, Germany
6 Frauenheilkunde und Geburtshilfe, Universität Regensburg, Regensburg, Germany
7 Institut für Humangenetik, Universität Bonn, Zentrum für erbliche Tumorerkrankungen, Universitätsklinikum Bonn, Bonn, Germany
8 Frauenheilkunde, Uniklinik Köln, Köln, Germany
9 Frauenklinik, Universitätsspital Basel, Basel, Switzerland
10 Klinik für Innere Medizin II, St.-Johannes-Hospital Dortmund, Dortmund, Germany
11 Interdisziplinäres Zentrum Palliativmedizin, Universitätsklinikum Würzburg, Würzburg, Germany
12 Xcare, Praxis für Strahlentherapie, Saarlouis, Saarlouis, Germany
13 Klinik für Strahlentherapie und Radioonkologie, Vivantes Klinikum Neukölln, Berlin, Germany
14 Zentrum für Innere Medizin, Universitätsklinikum Heidelberg, Heidelberg, Germany
15 Frauenklinik, HELIOS-Klinikum Krefeld, Krefeld, Germany
16 Praxis für Frauenheilkunde Hamburg, Hamburg, Germany
17 Facharzt für Radiologie und Strahlentherapie, Wiesbaden, Germany
18 Institut für Pathologie, Universitätsklinikum Leipzig, Leipzig, Germany
19 Klinik für Frauenheilkunde, Universitätsklinikum Freiburg, Freiburg, Germany
20 Klinik für Allgemein-, Gefäß- und Viszeralchirurgie, Martin-Luther-Krankenhaus, Berlin, Germany
21 Muldentalkliniken, Grimma, Germany

22 Dept. of OB/Gyn, University Hospital Erlangen, Erlangen, Germany
23 Women's Department, University Hospital of Essen, Essen, Germany
24 Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie, Charité, Campus Benjamin Franklin, Universitätsmedizin Berlin, Berlin, Germany
25 Klinik für Nuklearmedizin, Pius Hospital Oldenburg, Oldenburg, Germany
26 Klinik für Palliativmedizin, Universitätsmedizin Göttingen, Göttingen, Germany
27 Obstetrics and Gynecology, Reproductive Medicine, University of Muenster, Germany, Münster, Germany
28 Institut für Diagnostische und Interventionelle Radiologie, Universitätsmedizin Göttingen, Göttingen, Germany
29 Frauenselbsthilfe nach Krebs e. V., Erlangen, Erlangen/Forchheim, Germany
30 MGZ – Medizinisch Genetisches Zentrum, München und Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, München, Germany
31 Institut für Humangenetik, Universitätsklinikum Düsseldorf, Düsseldorf, Germany
32 Frauenklinik Charité, Campus Virchow-Klinikum, Universitätsmedizin Berlin, Berlin, Germany
33 Frauenheilkunde, Medizinische Universität Innsbruck, Innsbruck, Austria
34 Frauenklinik Nathanstift – Klinikum Fürth, Fürth, Germany
35 Stiftungsprofessur Selbsthilfeforschung, Tumorzentrum/CCC Freiburg, Universitätsklinikum Freiburg, Freiburg, Germany
36 Universitätsklinik für Frauenheilkunde, Inselspital Bern, Bern, Switzerland
37 Praxis für Physiotherapie, Hannover, Germany
38 Center for Familial Breast and Ovarian Cancer, University Hospital of Cologne, Cologne, Germany
39 Frauenklinik am Klinikum rechts der Isar, München, Germany
40 Mammazentrum, Krankenhaus Jerusalem, Hamburg, Germany
41 Medizinischer Dienst des Spitzenverbandes Bund der Krankenkassen e. V., Essen, Germany
42 Strahlenklinik, Universitätsklinikum Erlangen, CCC ER-EMN, Universitäts-Brustzentrum Franken, Erlangen, Germany
43 Deutsche Rentenversicherung Bund, Berlin, Germany
44 Winkelwaldklinik Nordrach, Fachklinik für onkologische Rehabilitation, Nordrach, Germany
45 Strahlenklinik, Sana Klinikum Offenbach, Offenbach, Germany
46 Pathologisches Institut, LMU München, München, Germany
47 Frauenklinik Klinikum Harlaching, München, Germany
48 Universitätsklinik für Radiologie und Nuklearmedizin, Universitätsklinikum Magdeburg, Magdeburg, Germany
49 Frauenselbsthilfe nach Krebs e. V., Bad Soden, Germany
50 Universitätsmedizin Greifswald, Greifswald, Germany
51 Frauenheilkunde, Medizinische Universität Graz, Graz, Austria
52 Klinikum für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany
53 Frauenklinik des Universitätsspitals Basel, Basel, Switzerland
54 Deutscher Verband für Physiotherapie, Referat Bildung und Wissenschaft, Köln, Germany
55 Landesfrauenklinik, HELIOS Universitätsklinikum Wuppertal, Wuppertal, Germany
56 Klinik für Frauenheilkunde, Geburtshilfe und Reproduktionsmedizin, Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes, Homburg, Saar, Germany
57 Institut für Pathologie, Landeskrankenhaus Graz West, Graz, Austria
58 Frauenklinik, Universitätsklinikum Jena, Jena, Germany
59 Marien Hospital Herne – Universitätsklinikum der Ruhr-Universität Bochum, Herne, Germany
60 AWMF-IMWi, AWMF, Berlin, Germany
61 Deutsche Krebsgesellschaft, Office des Leitlinienprogramms Onkologie, Berlin, Germany
62 Institut für Klinische Epidemiologie & Biostatistik (CEB), Basel, Switzerland
63 Deutsche Krebsgesellschaft e. V., Berlin, Germany

Key words
endometrial cancer, epidemiology, genetics, guideline, screening, hereditary factors

Schlüsselwörter
Endometriumkarzinom, Epidemiologie, Genetik, Leitlinie, Screening, erbliche Faktoren

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Correspondence
Prof. Dr. med. Günter Emons
Georg-August-Universität Göttingen, Universitätsmedizin Göttingen, Klinik für Gynäkologie und Geburtshilfe
Robert-Koch-Straße 40, 37075 Göttingen, Germany
emons@med.uni-goettingen.de

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ABSTRACT

Summary The first German interdisciplinary S3-guideline on the diagnosis, therapy and follow-up of patients with endometrial cancer was published in April 2018. Funded by German Cancer Aid as part of an Oncology Guidelines Program, the lead coordinators of the guideline were the German Society of Gynecology and Obstetrics (DGGG) and the Gynecological Oncology Working Group (AGO) of the German Cancer Society (DKG).

Purpose The use of evidence-based, risk-adapted therapy to treat low-risk women with endometrial cancer avoids unnecessarily radical surgery and non-useful adjuvant radiotherapy and/or chemotherapy. This can significantly reduce therapy-induced morbidity and improve the patient's quality of life as well as avoiding unnecessary costs. For women with endometrial cancer and a high risk of recurrence, the guideline defines the optimal surgical radicality together with the appropriate chemotherapy and/or adjuvant radiotherapy where required. The evidence-based optimal use of different therapeutic modalities should improve survival rates and the quality of life of these patients. The S3-guideline on endometrial cancer is intended as a basis for certified gynecological cancer centers. The aim is that the quality indicators established in this guideline will be incorporated in the certification processes of these centers.

Methods The guideline was compiled in accordance with the requirements for S3-level guidelines. This includes, in the first instance, the adaptation of source guidelines selected using the DELBI instrument for appraising guidelines. Other consulted sources include reviews of evidence which were compiled from literature selected during systematic searches of literature databases using the PICO scheme. In addition, an external biostatistics institute was commissioned to carry out a systematic search and assessment of the literature for one area of the guideline. The identified materials were used by the interdisciplinary working groups to develop suggestions for Recommendations and Statements, which were then modified during structured consensus conferences and/or additionally amended online using the DELPHI method with consent being reached online. The guideline report is freely available online.

Recommendations Part 1 of this short version of the guideline presents recommendations on epidemiology, screening, diagnosis and hereditary factors, The epidemiology of endometrial cancer and the risk factors for developing endometrial cancer are presented. The options for screening and the methods used to diagnose endometrial cancer including the pathology of the cancer are outlined. Recommendations are given for the prevention, diagnosis, and therapy of hereditary forms of endometrial cancer.

ZUSAMMENFASSUNG

Zusammenfassung Im April 2018 erschien die erste deutsche interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge der Patientinnen mit Endometriumkarzinom. Von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert, wurde sie von der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) und der Arbeitsgemeinschaft Onkologische Gynäkologie (AGO) der Deutschen Krebsgesellschaft (DKG) federführend koordiniert.

Ziele Durch eine evidenzbasierte risikoadaptierte Therapie können bei den Frauen mit Endometriumkarzinom mit geringem Risiko eine unnötige Radikalität bei der Operation und nicht sinnvolle adjuvante Strahlen- und/oder Chemotherapie vermieden werden. Dies reduziert zum einen deutlich die therapieinduzierte Morbidität und erhöht die Lebensqualität der Patientinnen. Auf der anderen Seite werden unnötige Kosten vermieden. Für die Frauen mit einem Endometriumkarzinom mit hohem Rezidivrisiko definiert die Leitlinie die optimale operative Radikalität sowie die ggf. erforderliche Chemotherapie und/oder adjuvante Strahlentherapie. Durch den evidenzbasierten optimalen Einsatz der verschiedenen Therapiemodalitäten sollten Überleben und Lebensqualität dieser Patientinnen verbessert werden. Die S3-Leitlinie zum Endometriumkarzinom soll eine Grundlage für die Arbeit der zertifizierten gynäkologischen Krebszentren sein. Die auf dieser Leitlinie basierenden Qualitätsindikatoren sollen in den Zertifizierungsprozess dieser Zentren einfließen.

Methoden Die Leitlinie wurde gemäß den Anforderungen eines S3-Niveaus erarbeitet. Dies umfasst zum einen die Adaptation der mittels des DELBI-Instruments selektierten Quellleitlinien. Zum anderen Evidenzübersichten, die anhand der in systematische Recherchen nach dem PICO-Schema in ausgewählten Literaturdatenbanken selektierten Literatur erstellt wurden. Ergänzend wurde ein externes Biostatistik-Institut mit der systematischen Literaturrecherche und -Bewertung eines Teilbereichs beauftragt. Diese Ergebnisse dienten den interdisziplinären Arbeitsgruppen als Basis für die Erarbeitung von Vorschlägen für Empfehlungen und Statements, welche in strukturierten Konsensuskonferenzen und/oder ergänzend im DELPHI-Verfahren auch online modifiziert und konsentiert wurden. Der Leitlinienreport ist online frei verfügbar.

Empfehlungen Der Teil 1 dieser Kurzversion der Leitlinie zeigt Empfehlungen zur Epidemiologie, Früherkennung, Diagnostik und hereditären Faktoren: Die Epidemiologie des Endometriumkarzinoms und Risikofaktoren für seine Entstehung werden dargestellt. Die Möglichkeiten der Früherkennung und die Methoden der Diagnostik des Endometriumkarzinoms, einschließlich der Pathologie, werden behandelt. Es werden Empfehlungen zur Prävention, Diagnostik und Therapie von hereditären Formen des Endometriumkarzinoms gegeben.

Thieme

I Guideline Information

Editors

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

Lead professional societies

The German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, DGGG) and the German Cancer Society (Deutsche Krebsgesellschaft, DKG) represented by the Gynecological Oncology Working Group (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO).

This guideline was developed in cooperation with the Guideline Program of the DGGG, OEGGG and SGGG. For further information see bottom of this article.

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▶ **Table 1** Steering committee.

	Name	City
1.	Prof. Dr. med. Günter Emons (guideline coordinator)	Göttingen
2.	Prof. Dr. med. Eric Steiner (deputy guideline coordinator)	Rüsselsheim
3.	Dr. med. Nina Bock (editor)	Göttingen
4.	Kerstin Paradies	Hamburg
5.	Dr. med. Christoph Uleer	Hildesheim
6.	Prof. Dr. med. Dirk Vordermark	Halle/Saale

Guideline documents

The complete long version together with a summary of the conflicts of interest of all of the authors, a short version, the guideline report, and the search for external literature are available in German on the homepage of the Oncology Guidelines Program under: https://www.leitlinienprogramm-onkologie.de/leitlinien/endometriumkarzinom/, last accessed on 13.08.2018.

Guideline authors

The working groups who contributed to this guideline consisted of members of the guideline steering committee (▶ **Table 1**), specialists nominated by participating professional societies and organizations (▶ **Table 2**), and experts invited to participate by the steering committee (▶ **Table 3**), and they are the authors of this guideline. Only mandate holders nominated by participating professional societies and organizations were eligible to vote on a chapter-by-chapter basis during the voting process (consensus

▶ **Table 2** Participating professional societies and organizations.

Participating professional societies and organizations	Mandate holder	Deputy
ADT (Association of German Tumor Centers [AG Deutscher Tumorzentren])	**Prof. Dr. med. Olaf Ortmann**, Regensburg	
AET (DKG Working Group for Hereditary Tumor Disease [AG Erbliche Tumorerkrankungen der DKG])	**Prof. Dr. med. Stefan Aretz**, Bonn	**Prof. Dr. med. Rita Katharina Schmutzler**, Köln **Prof. Dr. med. Alfons Meindl**, Munich (only once in 06/2015)
AGO (Gynecological Oncology Working Group of the DGGG and DKG [Arbeitsgemeinschaft Gynäkologische Onkologie in der DGGG und DKG])	**Prof. Dr. med. Peter Mallmann**, Cologne	
AGO Study Group (Arbeitsgemeinschaft Gynäkologische Onkologie [AGO] Studiengruppe)	**PD Dr. med. Christian Kurzeder**, Basel	**Prof. Dr. med. Felix Hilpert**, Hamburg
AIO (Internal Oncology Working Group [Arbeitsgemeinschaft Internistische Onkologie der DKG])	**Dr. med. Volker Hagen**, Dortmund	**PD Dr. med. Anne Letsch**, Berlin
APM (Palliative Medicine Working Group of the German Cancer Society [Arbeitsgemeinschaft Palliativmedizin der Deutschen Krebsgesellschaft])	**Prof. Dr. med. Birgitt van Oorschot**, Würzburg	**Dr. med. Joan Elisabeth Panke**, Essen
ARO (Radiological Oncology Working Group [Arbeitsgemeinschaft Radiologische Onkologie der DKG])	**Prof. Dr. med. Stefan Höcht**, Saarlouis	**Prof. Dr. med. Vratislav Strnad**, Erlangen
ASORS (Supportive Measures in Oncology, Rehabilitation and Social Medicine Working Group [AG Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG])	**Prof. Dr. med. Petra Feyer**, Berlin **Prof. Dr. med. Gerlinde Egerer**, Heidelberg (till 10/2015)	**Dr. med. Christiane Niehues**, Berlin (02–10/2016) **Dr. med. Timm Dauelsberg**, Nordrach

Continued next page

▶ **Table 2** Participating professional societies and organizations. *(Continued)*

Participating professional societies and organizations	Mandate holder	Deputy
BLFG (Federal Association of Senior Physicians in Gynecology and Obstetrics [Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe])	**Prof. Dr. med. Michael Friedrich**, Krefeld	
BNGO (Professional Association of Gynecological Oncologists in Private Practice in Germany [Berufsverband Niedergelassener Gynäkologischer Onkologen in Deutschland])	**Dr. med. Christoph Uleer**, Hildesheim	
BVF (Professional Association of Gynecologists [Berufsverband der Frauenärzte])	**Dr. med. Wolfgang Cremer**, Hamburg	
BVDST (Federal Association of German Radiotherapists [Bundesverband Deutscher Strahlentherapeuten])	**Prof. Dr. med. Franz-Josef Prott**, Wiesbaden	**Prof. Dr. med. Peter Niehoff**, Offenbach
BV Pathologie (Federal Association of German Pathologists [Bundesverband Deutscher Pathologen])	**Prof. Dr. med. Lars-Christian Horn**, Leipzig	**Prof. Dr. med. Doris Mayr**, Munich
DEGRO (German Society for Radiation Oncology [Deutsche Gesellschaft für Radioonkologie])	**Prof. Dr. med. Dirk Vordermark**, Halle	
DEGUM (German Society for Ultrasound in Medicine [Deutsche Gesellschaft für Ultraschall in der Medizin])	**Prof. Dr. med. Heinrich Prömpeler**, Freiburg	**Prof. Dr. med. Dieter Grab**, Munich
DGAV (German Society for General and Visceral Surgery [Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie])	**Prof. Dr. med. Jan Langrehr**, Berlin	
DGCH (German Society of Surgery [Deutsche Gesellschaft für Chirurgie])	**Prof. Dr. med. Steffen Leinung**, Grimma († 25.11.2016)	
DGE (German Society of Endocrinology [Deutsche Gesellschaft für Endokrinologie])	**Prof. Dr. med. Matthias W. Beckmann**, Erlangen	
DGGG (German Society of Gynecology and Obsetrics [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe])	**Prof. Dr. med. Rainer Kimmig**, Essen	
DGHO (German Society of Hematology and Medical Oncology [Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie])	**PD Dr. med. Anne Letsch**, Berlin	**Dr. med. Volker Hagen**, Dortmund
DGN (German Society of Nuclear Medicine [Deutsche Gesellschaft für Nuklearmedizin])	**Prof. Dr. med. Michael J. Reinhardt**, Oldenburg	**Prof. Dr. med. Michael Kreißl**, Magdeburg
DGP (German Society for Palliative Medicine [Deutsche Gesellschaft für Palliativmedizin])	**Prof. Dr. med. Bernd Alt-Epping**, Göttingen	
DGP (German Society of Pathology [Deutsche Gesellschaft für Pathologie])	**Prof. Dr. med. Lars-Christian Horn**, Leipzig	**Prof. Dr. med. Doris Mayr**, Munich
DMG (German Menopause Society [Deutsche Menopause Gesellschaft])	**Prof. Dr. med. Ludwig Kiesel**, Münster	**Dr. med. Ralf Witteler**, Münster
DRG (German Roentgen Society [Deutsche Röntgengesellschaft])	**Prof. Dr. med. Jan Menke**, Göttingen	
FSH (Self-help Group for Women after Cancer [Frauenselbsthilfe nach Krebs])	**Marion Gebhardt**, Forchheim	**Annemarie Schorsch**, Bad Soden
GFH (German Society of Human Genetics [Deutsche Gesellschaft für Humangenetik])	**Dr. med. Verena Steinke-Lange**, Munich	**Dr. med. Nils Rahner**, Düsseldorf (einmalig 04/2016)
KOK (Working Group of the DKG: Conference of Oncological Nursing and Pediatric Nursing [Arbeitsgemeinschaft der DKG: Konferenz Onkologische Kranken- und Kinderkrankenpflege])	**Kerstin Paradies**, Hamburg	
NOGGO (Northeast German Society of Gynecological Oncology [Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie])	**Prof. Dr. med. Werner Lichtenegger**, Berlin	**Prof. Dr. med. Alexander Mustea**, Greifswald
OEGGG (Austrian Society of Gynecology and Obstetrics [Österreichische Gesellschaft für Gynäkologie und Geburtshilfe])	**Prof. Dr. med. Alain-Gustave Zeimet**, Innsbruck	**Prof. Dr. med. Edgar Petru**, Graz
PRiO (Prevention and Integrative Oncology Working Group of the DKG [Arbeitsgemeinschaft der DKG Prävention und integrative Medizin in der Onkologie])	**Prof. Dr. med. Volker Hanf**, Fürth	**Prof. Dr. med. Jutta Hübner**, Jena
PSO (German Psycho-oncology Working Group [Deutsche Arbeitsgemeinschaft für Psychoonkologie])	**Prof. Dr. phil. Joachim B. Weis**, Freiburg	**Dr. med. Anne D. Rose**, Berlin
SGGG (Swiss Society of Gynecology and Obstetrics [Schweizer Gesellschaft für Gynäkologie und Geburtshilfe])	**Prof. Dr. med. Michael D. Mueller**, Berne	**PD Dr. med. Edward Wight**, Basel
ZVK (Central Association of Physiotherapists [Zentralverband der Physiotherapeuten/Krankengymnasten])	**Ulla Henscher**, Hanover	**Reina Tholen**, Cologne

▶ **Table 3** Experts who contributed in an advisory capacity, methodological advisors and other contributors.

	City
Experts	
PD Dr. Dr. med. Gerd J. Bauerschmitz	Göttingen
Prof. Dr. med. Markus Fleisch	Düsseldorf
Prof. Dr. med. Ingolf Juhasz-Böss	Homburg/ Saar
Prof. Dr. med. Sigurd Lax	Graz
Prof. Dr. med. Ingo Runnebaum	Jena
Prof. Dr. med. Clemens Tempfer	Herne
Methodological advice	
Dr. med. Monika Nothacker, MPH, AWMF Institute for Medical Knowledge Management (AWMF-IMWi)	Berlin
Dipl. Biol. Susanne Blödt, MScPH, AWMF Institute for Medical Knowledge Management (AWMF-IMWi)	Berlin
Dr. med. Markus Follmann, MPH, MSc, Office of the Oncology Guidelines Program c/o DKG	Berlin
Dipl.-Soz.Wiss Thomas Langer, Office of the Oncology Guideline Program c/o DKG	Berlin
Dr. med. Heike Raatz, MSc, Basel Institute for Clinical Epidemiology & Biostatistics (compilation of an evidence report, see guideline documents)	Basel
Dr. med. Simone Wesselmann, MBA, German Cancer Society – Certification Department (coordination of the compilation of quality indicators)	Berlin
Other contributors	
Dr. med. Nina Bock (guideline secretariat, guideline assessment, selection and assessment of the literature)	Göttingen
Saskia Erdogan (guideline secretariat, assessment of the literature)	Göttingen

process) after they had disclosed and excluded any conflicts of interest [1]. The guideline was compiled with the direct participation of two patient representatives.

Physicians of the Competence Oncology Center of the National Association of Statutory Health Insurance Funds (Kompetenz Centrum Onkologie des GKV-Spitzenverbandes) and the Medical Service of German Health Funds (MDK-Gemeinschaft) were involved in an advisory capacity during the formulation of specific aspects of this S3-guideline which were relevant for social medicine.

They did not participate in the voting on individual recommendations and are not responsible for the contents of this guideline.

Abbreviations

ACR	American College of Radiology
AEH	atypical endometrial hyperplasia
AG	working group (Arbeitsgruppe)
AWMF	Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.)
ÄZQ	Medical Center for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin)
BMI	body mass index
CEB	Basel Institute for Clinical Epidemiology & Biostatistics of the University of Basel
CEBM	Centre for Evidence-Based Medicine (Oxford, UK)
CS	Cowden syndrome
CT	computed tomography
DELBI	German Guideline Assessment Instrument
DELPHI	multistage survey method
DKG	German Cancer Society (Deutsche Krebsgesellschaft e. V.)
DKH	German Cancer Aid (Deutsche Krebshilfe e. V.)
EC	expert consensus
FIGO	International Federation of Gynecology and Obstetrics
GoR	grade of recommendation
HCS	hereditary cancer syndrome
HNPCC	hereditary non-polyposis colorectal cancer
HT/HRT	hormone therapy in perimenopause and post-menopause (hormone replacement therapy)
IKNL	Integraal Kankercentrum Nederland
LoE	level of evidence
LS	Lynch syndrome
MMR	mismatch repair
MMMT	malignant Müllerian mixed tumor/malignant mesodermal mixed tumor: carcinosarcoma
MRI	magnetic resonance imaging
OL	Oncology Guidelines Program
PCOS	polycystic ovarian syndrome
PET-CT	positron emission tomography + computed tomography
PHTS	PTEN hamartoma tumor syndrome
PMB	postmenopausal bleeding
SEE-FIM	section and extensively examine the FIMbriated end of the fallopian tube
ST	statement
UICC	Union internationale contre le cancer
WHO	World Health Organization

II Guideline Application

Purpose and objectives

The most important reason for compiling this interdisciplinary guideline is the high epidemiological significance of endometrial cancer and its associated burden of disease. Evidence-based risk-adapted therapy to treat low-risk women with endometrial cancer can avoid unnecessarily radical surgery and non-useful adjuvant radiotherapy and/or chemotherapy. This reduces therapy-induced morbidity, improves patients' quality of life and avoids unnecessary costs. For women with endometrial cancer and a high risk of recurrence, the guideline defines the optimal surgical radicality and the appropriate adjuvant chemotherapy and/or adjuvant radiotherapy. The evidence-based optimal use of different therapy modalities should improve survival rates and the quality of life of these patients.

Targeted areas of patient care

The guideline covers outpatient and inpatient care.

Target patient groups

The recommendations of the guideline are aimed at all women with endometrial cancer and their relatives.

Target user groups

The recommendations of the guideline are addressed to all physicians and professionals who provide care to patients with endometrial cancer. In the first instance, this group includes gynecologists, general practitioners, radiologists, pathologists, radio-oncologists, hematologists/oncologists, psycho-oncologists, palliative care professionals and nursing staff.

Other target groups are:

- Scientific medical societies and professional organizations;
- Advocacy groups for affected women (women's health organizations, patient and self-help organizations);
- Quality assurance institutions and projects at federal and *Länder* levels (AQUA, the Institute for Applied Quality Improvement and Research in Healthcare, the Association of German Tumor Centers, etc.);
- Health policy institutions and decision-makers at federal and *Länder* levels;
- Funding agencies.

Period of validity and update procedure

This guideline is valid from April 1, 2018 through to April 1, 2023. Regular updates are planned; if changes are urgently required, amendments will be developed which will be published in the latest version of the guideline. The aim is currently to update the guideline every two years.

III Methodology of the Guideline

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 1.1, https://www.awmf.org/leitlinien/awmf-regelwerk/awmf-regelwerk-offline.html, last accessed on 13.08.2018) differentiates between the lowest (S1), the intermediate (S2) and the highest (S3) class [4]. 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 subdivided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest class (S3) combines both approaches. This guideline is classified as: S3.

Grading of evidence

Identified trials used in this guideline were assessed using the 2011 version of the system developed by the Oxford Centre for Evidence-based Medicine. This classifies studies according to various clinical questions (benefit of therapy, prognostic value, diagnostic validity). Further information is available online at: http://www.cebm.net/index.aspx?o=5653, last accessed on 13.08.2018.

Grading of recommendations

The level of recommendation expresses the degree of certainty that the expected benefit of the intervention will outweigh the possible damage caused (net benefit) and that the expected positive effects will reach a level which will be relevant for the patient. Negative recommendations (must not) indicate the certainty that there will be no benefit or the result may potentially be damaging (▶ **Table 4**). The grading of recommendations incorporates the results of evaluated trials, the applicability of study results to target patient groups, the feasiblity in daily clinical practice and ethical obligations and patient preferences [2, 3].

▶ **Table 4** Grading of recommendations.

Level of recommendation	Description	Syntax
A	Strong recommendation	shall/shall not
B	Recommendation	should/should not
0	Recommendation open	may/can

Recommendations

Recommendations are thematically grouped key sentences with a recommendation for action, which were developed by the guideline group and voted on in a formal consensus procedure.

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.

Expert consensus (EC)

Recommendations for which no systematic systematic search of the literature was carried out are referred to as expert consensus (EC). As a rule, these recommendations cover approaches considered to be good clinical practice where no scientific studies are necessary or could be expected.

IV Guideline

1 Epidemiology and risk factors, prevention of endometrial cancer

1.1 Epidemiology and risk factors

1.1.1 Age

No.	Recommendation	GoR	LoE	Sources
3.1	The risk of developing endometrial cancer increases with age.	ST	1	[5]

1.1.2 Hormone therapy (HRT) without a progestogen for endometrial protection

No.	Recommendation	GoR	LoE	Sources
3.2	Hormone therapy with estrogens alone, without gestagen protection, is a risk factor for the development of endometrial cancer in women who have not undergone hysterectomy. The effect depends on the duration of administration.	ST	2	[6 – 11]

1.1.3 Hormone therapy with a progestogen for endometrial protection

1.1.3.1 Continuous combined estrogen-progestogen therapy

No.	Recommendation	GoR	LoE	Sources
3.3	A reduction in the risk of endometrial cancer was observed for women who received continuous combined hormone therapy with conjugated equine estrogens and medroxyprogesterone acetate as the progestogen over an average period of 5.6 years.	ST	2	[12]
3.3.1	Continuous combined hormone therapy administered for < 5 years may be considered safe with regard to the risk of developing endometrial cancer.	ST	2	6, 7, 9, 10, 12, 13, 14]

1.1.3.2 Long-term administration of continuous combined HRT

No.	Recommendation	GoR	LoE	Sources
3.4	An increased risk of developing endometrial cancer was observed following the long-term administration of continuous combined hormone therapy > 6 years or > 10 years.	ST	3	[9, 10]
3.5	The administration of progesterone or dydrogesterone in the context of continuous combined hormone therapy may increase the risk of developing endometrial cancer.	ST	3	[13]

1.1.3.3 Sequential combined estrogen/progestogen therapy

No.	Recommendation	GoR	LoE	Sources
3.6	Sequential combined hormone therapy may increase the risk of developing endometrial cancer. The effect depends on the duration, type and dosage of the administered progestogen.	ST	3	[6, 7, 9 – 11, 14]
3.7	Sequential combined hormone therapy administered for < 5 years which includes the administration of a synthetic progestogen for at least 12–14 days per month may be considered safe with respect to the risk of developing endometrial cancer.	ST	3	[6, 7, 11]

1.1.4 Tibolone

No.	Recommendation	GoR	LoE	Sources
3.8	An increased risk of developing endometrial cancer has been observed for tibolone.	ST	3	[6, 11, 15]

1.1.5 Tamoxifen

No.	Recommendation	GoR	LoE	Sources
3.9	Therapy with tamoxifen is a risk factor for developing endometrial cancer. The effect is dependent on the duration of administration.	ST	1	[17 – 20]

1.1.6 Oral contraceptives

No.	Recommendation	GoR	LoE	Sources
3.10	Oral contraceptives reduce the risk for the development of endometrial carcinoma. The strength of the effect is dependent on the duration of intake.	ST	2	[21, 22]

1.1.7 Ovarian stimulation therapy

No.	Recommendation	GoR	LoE	Sources
3.11	Ovarian stimulation therapy increases the risk of endometrial cancer compared to population-based controls, but not compared with infertile women.	ST	4	[23, 24]

1.1.8 Other biological risk factors

No.	Recommendation	GoR	LoE	Sources
3.12	Late age at menarche and late age at the birth of the last child are associated with a reduced risk of developing endometrial cancer; late onset of menopause is associated with an increased risk of developing endometrial cancer.	ST	3	[25 – 27]
3.13	Diabetes mellitus, disturbance of glucose tolerance, metabolic syndrome and polycystic ovary syndrome (PCOS) increase the risk of developing endometrial cancer.	ST	3	[28 – 42]
3.14	An increased body mass index (BMI) increases the risk of developing endometrial cancer.	ST	3	[43 – 48]
3.15	A positive family history of endometrial cancer and and/or colon cancer is associated with a higher risk of developing endometrial cancer.	ST	3	[49]

1.1.9 Risk-reducing factors

No.	Recommendation	GoR	LoE	Sources
3.16	Physical activity is associated with a reduced risk of developing endometrial cancer.	ST	3	[50 – 54]
3.17	The use of intrauterine devices (IUDs; copper spirals or therapeutic levonorgestrel spirals) is associated with a reduced risk of developing endometrial cancer.	ST	3	[55, 56]

2 Screening and Diagnosis of Endometrial Cancer

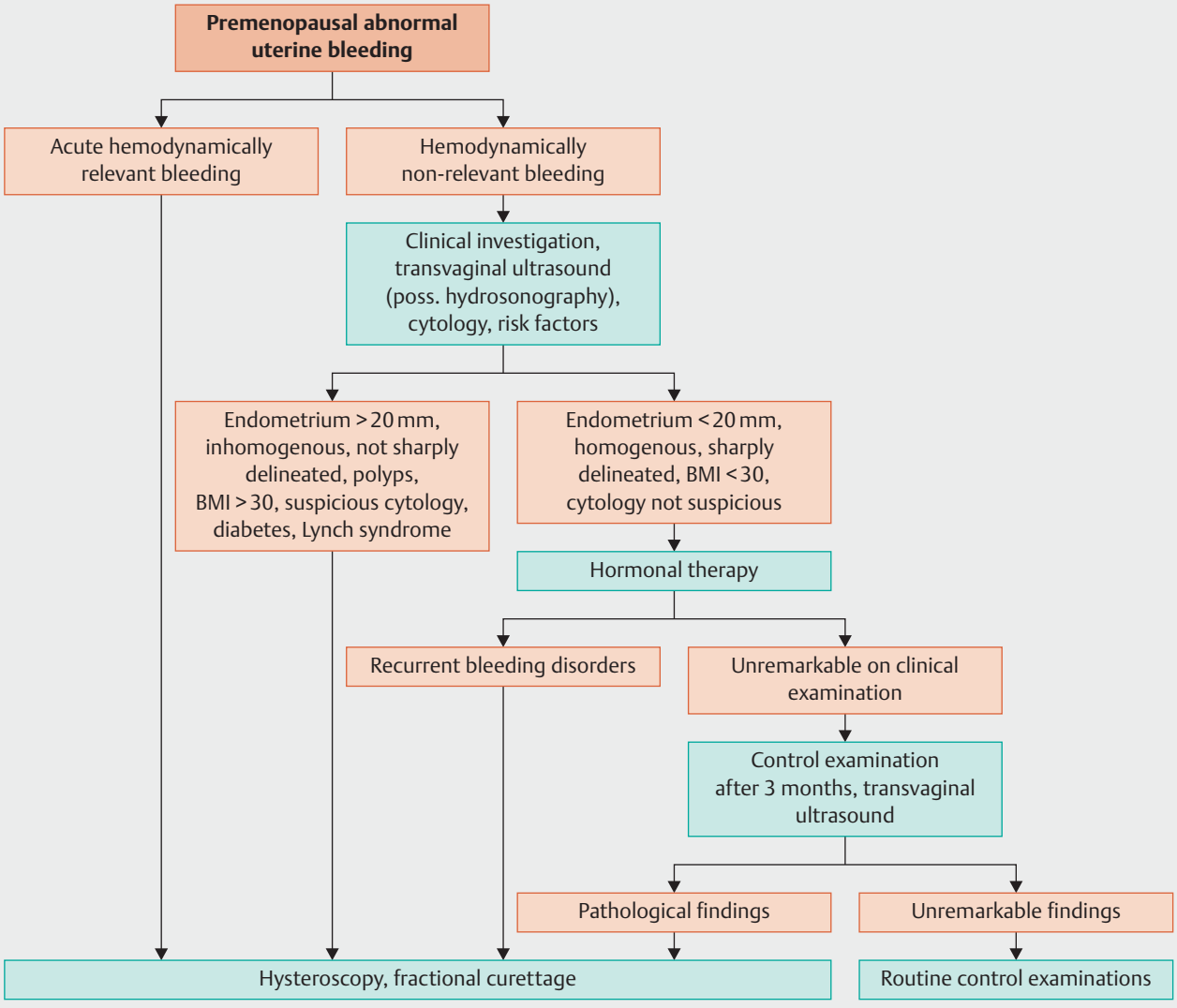
2.1 Screening/diagnosis of asymptomatic women

2.1.1 Asymptomatic women with no increased risk

No.	Recommendation	GoR	LoE	Sources
4.1	The available data do **not** show that screening using transvaginal ultrasound in asymptomatic women with no increased risk of endometrial cancer reduces endometrial cancer-specific mortality.	EC		
4.2	Transvaginal ultrasonography must not be carried out for purposes of early detection of endometrial cancer in asymptomatic women who are not at increased risk for endometrial carcinoma.	EC		

2.1.2 Asymptomatic women with an increased risk

No.	Recommendation	GoR	LoE	Sources
4.3	The available data do not show that transvaginal ultrasound screening in asymptomatic women who have an increased risk of developing endometrial cancer (e.g., women with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS) reduces endometrial cancer-specific mortality.	EC		
4.4	The available data do not show that screening of asymptomatic women who have an increased risk of developing endometrial cancer (e.g., women with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS) using endometrial biopsy, pipelle sampling, Tao brush cytology, tumor marker sampling, fractional curettage or hysteroscopy reduces endometrial cancer-specific mortality.	ST	4	[57, 58]
4.5	Transvaginal ultrasound examinations must not be carried out for early detection of endometrial carcinoma in asymptomatic women who are at increased risk for endometrial carcinoma (such as those with Lynch syndrome, obesity, diabetes mellitus, hormone therapy, metabolic syndrome, PCOS).	EC		



BMI: Body Mass Index

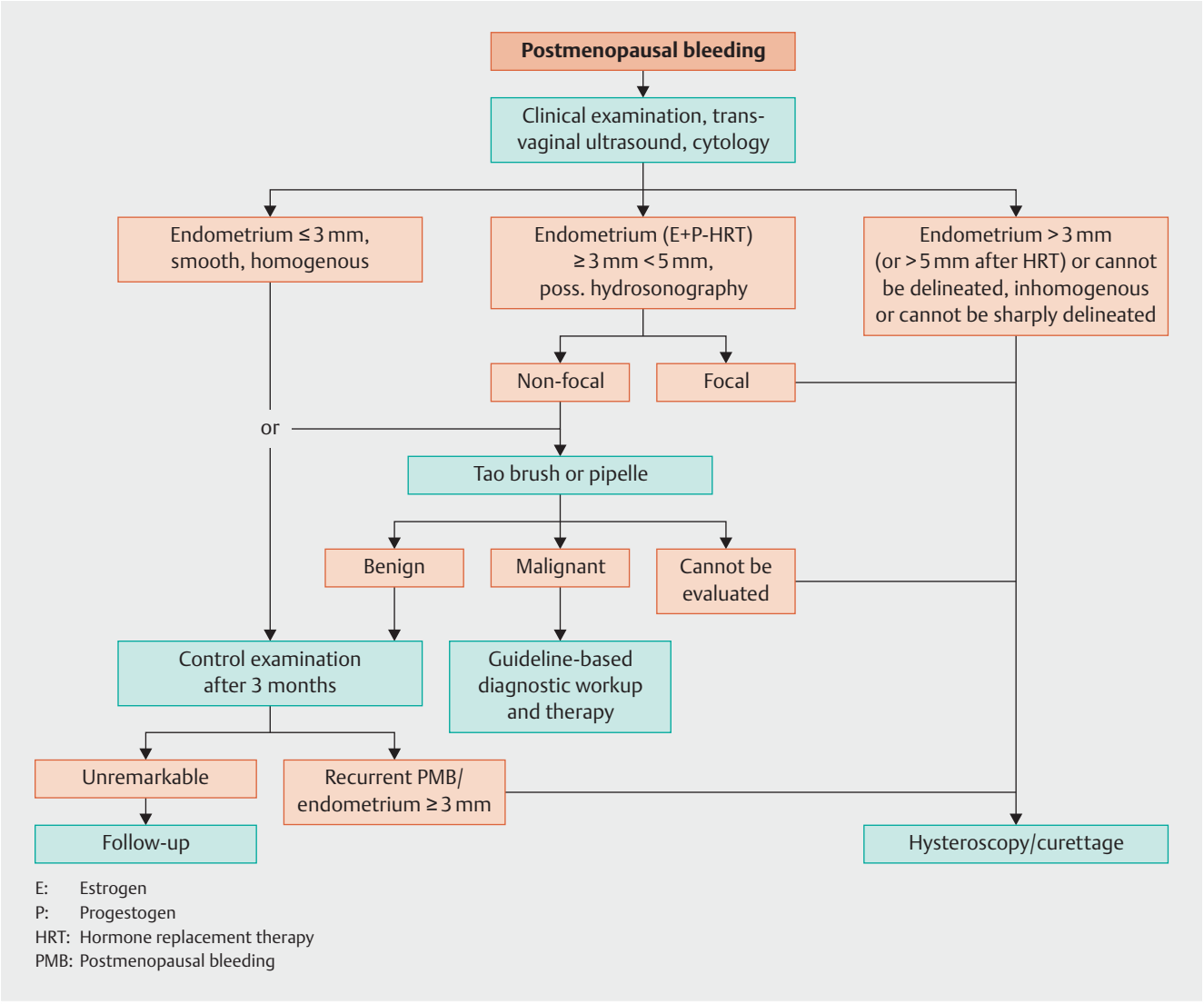
▶ **Fig. 1** Algorithm for "Investigating abnormal premenopausal uterine bleeding" [80]. [rerif]

2.1.3 Asymptomatic women and tamoxifen therapy

No.	Recommendation	GoR	LoE	Sources
4.6	Asymptomatic patients receiving tamoxifen therapy must **not** be examined by transvaginal ultrasound to screen for endometrial cancer.	A	3	[59 – 63]

2.2 Investigations for abnormal premenopausal uterine bleeding

No.	Recommendation	GoR	LoE	Sources
4.7	The risk of premenopausal women with abnormal uterine bleeding developing endometrial cancer or atypical endometrial hyperplasia is below 1.5 %.	ST	2	[64]
4.8	In women with premenopausal abnormal uterine bleeding who do not have any risk factors (suspicious cytology, obesity, Lynch syndrome, diabetes, polyps, etc.), an attempt at conservative treatment should initially be made, provided that the bleeding is not hemodynamically relevant. If conservative therapy fails, hysteroscopy/curettage should be carried out.	EC		
4.9	Hysteroscopy combined with fractional curettage is the gold standard for obtaining a reliable diagnosis of endometrial cancer.	ST	3	[65 – 67]



▶ **Fig. 2** Algorithm for "Diagnostic approach when bleeding occurs in perimenopausal or postmenopausal women" [80]. [rerif]

No.	Recommendation	GoR	LoE	Sources
4.10	In a number of small series of symptomatic patients, diagnostic procedures such as pipelle sampling and Tao brush cytology offered positive and negative predictive values for diagnosing endometrial cancer which were comparable to those obtained with curettage plus hysteroscopy. However, larger comparative studies are still lacking.	ST	3	[68]
4.10.1	These diagnostic procedures are not at present comprehensively available on a quality-assured basis throughout Germany.	EC		

2.3 Procedures for postmenopausal bleeding (PMB)

No.	Recommendation	GoR	LoE	Sources
4.11	When a woman presents with PMB for the first time and her endometrial thickness is ≤ 3 mm, then she should undergo sonographic and clinical examination after three months.	B	1	[69]
4.12	Histological investigations must be carried out if the clinical symptoms persist or reoccur or if there is an increase in endometrial thickness.	EC		

2.4 Diagnostic imaging procedures

2.4.1 General remarks on imaging procedures

No.	Recommendation	GoR	LoE	Sources
4.13	Surgical staging with histopathological evaluation is the reference method used to diagnose the local spread of endometrial cancer. Imaging is the primary diagnostic method used to detect distant metastases outside the usual surgical area.	EC		

2.4.2 Basic diagnostic imaging procedures

2.4.2.1 Chest X-ray

The IKNL and ACR guidelines recommend taking chest X-rays in 2 different views when making a primary diagnosis of endometrial cancer [71, 72]. It is a basic investigative procedure which primarily aims to assess the patient's cardiopulmonary status preoperatively and to detect and evaluate any rare pulmonary metastases. Preoperative chest radiographs show initial findings which can be used during potential follow-up examinations.

Although pulmonary metastases are rare at the first manifestation of endometrial cancer, they lead to FIGO stage IV. In a retrospective multicenter study, Amkreutz et al. [73] reported that pulmonary metastases of endometrial cancer were detected in the chest radiographs of 1.3% (7 of 541) patients. All affected patients had high-risk subtypes of endometrial cancer (serous, clear-cell or poorly differentiated endometrioid), and the incidence of pulmonary metastases was 4.1% for these subtypes. No pulmonary metastases were detected in the chest radiographs of patients with low-risk endometrial cancer subtypes. 243 patients did not undergo thoracic imaging as a primary diagnostic procedure. The authors concluded that thoracic imaging was not required to detect metastasis in patients with low-risk subtypes of endometrial cancer. According to the study by Amkreutz et al. [73], around 4% of patients with high-risk subtypes had pulmonary metastasis. and the detection of metastases could be therapeutically relevant for these patients.

2.4.2.2 Abdominal ultrasound

Abdominal ultrasound is part of the basic workup, particularly to assess the internal organs including any possible preexisting urinary transport disorder. Evaluating the lesser pelvis and the retroperitoneum is difficult because of the superimposition of intestinal gases. This guideline concurs with the ACR guideline [72] which considers transabdominal ultrasound to be an unsuitable method for staging endometrial cancer.

2.4.2.3 Transvaginal ultrasound

No.	Recommendation	GoR	LoE	Sources
4.14	After obtaining histological confirmation of primary endometrial cancer, transvaginal ultrasound should be carried out to evaluate the extent of myometrial infiltration and cervical infiltration.	B	3	[70]
4.15	Preoperative imaging using transvaginal ultrasound is done to document findings and plan the surgical procedure, even if definitive loco-regional staging is only possible following histological examination after surgery.	EC		

2.4.3 Tomography as a diagnostic workup method to determine local spread

No.	Recommendation	GoR	LoE	Sources
4.16	If the transvaginal ultrasound findings show limited imaging quality, magnetic resonance imaging (MRI) should be offered for preoperative assessment of the extent of infiltration into the myometrium and cervix in patients with primary endometrial carcinoma.	B	3	[70]
4.17	Tomography should be carried out if non-invasive assessment of loco-regional lymph nodes is necessary.[1,2]	B	3	[71, 72, 74–77]
4.18	For primary radiotherapy, MRI should be used for the diagnostic workup to determine the extent of local spread, where possible.[3]	EC		

[1] For example, as a diagnostic imaging workup method prior to primary radiotherapy or to plan the surgical procedure in patients with advanced disease (cT3).

[2] Transabdominal and transvaginal ultrasound are not suitable for this.

[3] If carrying out an MRI is not possible, then the alternatives are either CT or PET-CT.

2.4.4 Imaging procedures for distant metastasis

No.	Recommendation	GoR	LoE	Sources
4.19	If there is a reasonable suspicion of distant metastasis, tomography (and bone scintigraphy if necessary) should be carried out to evaluate distant metastasis and plan treatment.	B	3	[71, 72, 76]

2.5 Pathology

▶ **Table 5** The dualistic model of endometrial cancer.

	Type I endometrial cancer	Type II endometrial cancer
Estrogen-associated	yes	no
Endometrium	usually hyperplastic	usually atrophic; SEIC
Receptor positivity (estrogens/progesterone)	usually positive	usually negative or weakly positive
Age	55–65 years	65–75 years
Prognosis	depends on the stage, usually favorable	depends on the stage, usually poor
Stage	usually FIGO stage I	usually FIGO stage II–IV
Histological subtype	endometrioid + variants; mucinous	serous, clear-cell
Molecular alterations	PTEN inactivation microsatellite instability β-catenin mutations K-ras mutations	p53 mutations E-cadherin inactivation PIK3CA alterations
Molecular types (TCGA)	POLE ultramutated, microsatellite instability hypermutated, copy number low	copy number high (serous-like)

▶ **Table 6** 2014 WHO classification of endometrial hyperplasia compared to earlier classifications [78].

Dallenbach-Hellweg classification	1994/2003 WHO classification	2014 WHO classification
Glandular cystic hyperplasia Grade 1 adenomatous hyperplasia	Simple hyperplasia without atypia	Endometrial hyperplasia without atypia
Grade 2	Complex hyperplasia without atypia	
Grade 3	Simple atypical endometrial hyperplasia Complex atypical endometrial hyperplasia	Atypical endometrial hyperplasia/EIN*

* EIN = endometrial intraepithelial neoplasia

2.5.1 Morphology of endometrial cancer

No.	Recommendation	GoR	LoE	Sources
4.20	The terminology and morphological workup of endometrial hyperplasia must be based on the most current version of the WHO classification.	EC		
4.21	Carcinosarcomas (malignant Müllerian mixed tumors, MMMT) are classified as carcinomas based on their molecular pathology. The histological evaluation of carcinosarcomas must be done in accordance with the most recent effective WHO classification. FIGO and TNM staging must be done in the same way as for endometrial cancer.	EC		

▶ **Table 7** Histopathological classification of endometrial cancer [78, 79].

Endometrioid adenocarcinoma
Endometrioid adenocarcinoma variants ▪ secretory variant ▪ ciliated cell variant ▪ villoglandular variant ▪ variant with squamous differentiation
Mucinous adenocarcinoma
Serous adenocarcinoma
Clear-cell adenocarcinoma
Mixed carcinoma
Undifferentiated carcinoma ▪ monomorphic type ▪ dedifferentiated type
Neuroendocrine tumors ▪ well differentiated neuroendocrine tumor (carcinoid) ▪ poorly differentiated small-cell neuroendocrine carcinoma ▪ poorly differentiated large-cell neuroendocrine carcinoma
Other carcinomas

Carcinosarcomas of the endometrium used to be discussed in the S2K-guideline “Sarcomas of the Uterus”, Version 1.0, 2015, AWMF Registry Number: 015/074, http://www.awmf.org/leitlinien/detail/ll/015-074.html; they are now described in the S3-guideline “Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer” [80].

2.5.2 Staging of endometrial cancer

No.	Recommendation	GoR	LoE	Sources
4.22	Staging of endometrial cancers must be done in accordance with the most recent FIGO/TNM classifications.	EC		

2.5.3 Frozen section analysis for endometrial cancer, malignant Müllerian mixed tumors and AEH

No.	Recommendation	GoR	LoE	Sources
4.23	Intraoperative histological examination may be carried out if there is a suspicion of stage pT1b and/or pT2 disease.	EC		
4.24	If the surgeon is of the opinion that frozen section analysis is needed to assess the depth of myometrial infiltration and/or infiltration of the endocervical stroma of the endometrial cancer, then these two parameters must be assessed macroscopically and microscopically.	EC		
4.25	Frozen section analysis must not be carried out for the purpose of grading or to determine the histological tumor type.	EC		
4.26	The fallopian tubes and ovaries must be assessed macroscopically during intraoperative frozen section analysis; findings suspicious for metastasis must be examined histologically.	EC		

2.5.4 Tissue workup

No.	Recommendation	GoR	LoE	Sources
4.27	Tissue samples obtained by (fractional) curettage or endometrial biopsy must be completely embedded.	EC		
4.28	The report on the findings of (fractional) curettage or endometrial biopsy must provide information on the evidence for and type of endometrial hyperplasia. If a carcinoma is detected, its histological tumor type must be defined based on the current WHO classification. If there is evidence of tumor tissue in the cervical part of the fractional curettage specimen, every effort must be made to find evidence of or exclude endocervical stroma infiltration.	EC		
4.29	The morphological workup of hysterectomy specimens must be carried out in such a way that all therapeutically and prognostically relevant parameters can be determined. The diagnostic workup must be based on the currently valid WHO classification of tumor types and the current TNM classification for staging.	EC		
4.30	The report on findings for hysterectomy specimens obtained from patients with endometrial cancer must include the following information: ▪ histological type according to the WHO classification ▪ for mixed tumors: information about the ratio (percentage) of the specimen compared to the overall tumor ▪ the tumor grade ▪ evidence/absence of lymph node invasion or vascular invasion (L and V status) ▪ evidence/absence of perineural invasion (Pn status) ▪ staging (pTNM) ▪ metric information about the depth of invasion compared to the myometrial thickness, in mm ▪ three-dimensional tumor size, in cm ▪ if vaginal invasion is present, metric data about the minimum distance to the vaginal resection margin ▪ R classification (UICC)	EC		
4.31	According to the WHO classification, mixed carcinomas of the endometrium are defined as tumors with two or more histological subtypes which are found in > 5 % of the total tumor area on microscopic examination. The histological report on the findings must include the respective percentages of the individual histological subtypes.	EC		

2.5.5 Workup and diagnosis of omentectomy specimens in endometrial cancer

No.	Recommendation	GoR	LoE	Sources
4.32	The ovaries of patients with endometrial cancer should be completely embedded and must include the hilum of the ovary. The workup of the fallopian tubes should be guided by the SEE-FIM protocol.	EC		

No.	Recommendation	GoR	LoE	Sources
4.33	At least one representative paraffin block must be investigated during the pathological workup of an omentectomy specimen from a patient with endometrial cancer and macroscopic tumor infiltration. Four to six paraffin blocks (several sections can be embedded in a single block) must be examined if there is no macroscopic tumor infiltration. All other abnormal findings (e.g. intraomental lymph nodes) must be studied macroscopically and examined histologically.	EC		

2.5.6 Workup and diagnosis of lymphadenectomy specimens in endometrial cancer

No.	Recommendation	GoR	LoE	Sources
4.34	All resected lymph nodes in lymphadenectomy specimens obtained during surgery of a patient with endometrial cancer must be completely embedded and examined histologically.	EC		
4.35	Lymph nodes with a maximum extent of up to approx. 0.3 cm should be embedded in their entirety and larger lymph nodes should be either halved along their longitudinal axis or sliced into sections and also completely embedded.	EC		
4.36	Isolated tumor cells are defined as the detection of individual tumor cells or tumor cell complexes with a maximum diameter of < 0.2 mm. Micrometastases are defined as the histological confirmation of tumor cells in lymph nodes with diameters of ≥ 0.2 mm but not bigger than 0.2 cm.	EC		
4.37	The report on the findings of lymphadenectomy specimens obtained from patients with endometrial cancer must include the following information: ▪ Information about the number of affected lymph nodes compared to the number of resected lymph nodes mapped to the location where the respective lymph node was resected (pelvic, paraaortal), ▪ Information about the diameter of the largest lymph node metastasis in mm/cm, ▪ Information about the absence/evidence of any extracapsular spread of lymph node metastasis, ▪ Information about any evidence of isolated tumor cells in the lymph node as well as any evidence of lymph node invasion in perinodal fatty tissue and/or the lymph node capsule.	EC		

2.5.7 Sentinel lymph nodes (investigated in the context of clinical studies)

No.	Recommendation	GoR	LoE	Sources
4.38	In the setting of research studies, sentinel lymph nodes that are removed in patients with endometrial carcinoma must be fully embedded and examined in step sections. In addition, immunohistochemical examinations must be carried out ("ultrastaging") on sentinel lymph nodes that are negative on hematoxylin-eosin (HE) morphology.	EC		

2.5.8 Morphological prognostic factors

A detailed discussion of morphological prognostic factors is available (in German) in the long version of the guideline [80].

A risk stratification for endometrial cancer based morphological factors developed in consensus by the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO) is summarized in ▸ **Table 8** [81, 82].

▶ **Table 8** Risk stratification of endometrial cancer according to the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO) [81, 82].

Risk group	Characteristics
Low risk	endometrioid endometrial cancer, G1, G2, < 50 % myometrial infiltration, L0
Low-intermediate risk	endometrioid endometrial cancer, G1, G2, ≥ 50 % myometrial infiltration, L0
High-intermediate risk	endometrioid endometrial cancer, G3, < 50 % myometrial infiltration, L0 or L1 endometrioid endometrial cancer, G1, G2, L1, </≥ 50 % myometrial infiltration
High risk	endometrioid endometrial cancer, G3, ≥ 50 % myometrial infiltration, L0 or L1, FIGO/TNM stage II/T2 endometrioid endometrial cancer, FIGO/TNM stage III/T3, R0 non-endometrioid endometrial cancer (serous/clear-cell, undifferentiated, MMMT)

3 Hereditary Endometrial Cancer

3.1 Hereditary tumor syndrome with an increased risk of endometrial cancer

No.	Recommendation	GoR	LoE	Sources
10.1	Hereditary cancer syndromes (HCS) with a confirmed, significantly higher risk of developing endometrial cancer include Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC) and Cowden syndrome (CS) or PTEN hamartoma tumor syndrome (PHTS). Carriers of these HCS also have an increased risk of developing other syndrome-specific intestinal and extra-intestinal, benign and malignant tumors.	ST	3	[83 – 92]

▶ **Table 9** Tumor risks and mutation detection rates.

	Lynch syndrome (LS)	Cowden syndrome (CS)
Inheritance	autosomal-dominant	autosomal-dominant
Causative genes	MLH1, MSH2, MSH6, PMS2, EPCAM	PTEN
Frequency in the general population	**1 : 300–500**	1 : 200 000? [93]
Frequency in unselected patient cohorts with endometrial cancer	**2–4 %**	< 0.5 %
Frequency in patients with endometrial cancer < 50 years	**9–10 %**	
Endometrial cancer of the lower uterine segment	14–29 % [91]	
Spectrum of mutations in LS-associated endometrial cancer	PMS2: 5 %, MLH1: 16 % MSH2: 26 %, MSH6: 53 %	
Lifetime risk of endometrial cancer up to the 70th year of life (general population around 2.6 %) [107]	**Overall: 16–54 %** MLH1: 18–54 %, MSH2: 21–30 % MSH6: 16–49 %, PMS2: 12–15 % [83, 86, 94 – 97]	19–28 % [98, 99]
Average patient age at onset of LS-/CS-associated endometrial cancer (years)	**Overall: 50 years** MLH1: 44 (29–54), MSH2: 50 (36–66) MSH6: 55 (26–69), PMS2: 57 (44–69) [84, 87 – 89, 100]	48–53 [101, 102]
Metachronous cancer after a diagnosis of endometrial cancer	10 years: 25 %, 15 years: 50 %, 20 years: > 50 % [84, 85, 87, 103]	
Endometrioid type	57–85 %	84 % [102]
Other common tumors/tumor spectrum	colorectal cancer, duodenal cancer, gastric cancer, ovarian cancer, brain tumors, urothelial carcinoma	thyroid cancer, breast cancer, renal cancer, brain tumors, skin tumors

3.2 Risk determination

No.	Recommendation	GoR	LoE	Sources
10.2	An important tool for assessing a genetically caused increased risk of endometrial carcinoma is a medically obtained patient history and family history, taking specific clinical criteria into account (in Lynch syndrome: Amsterdam I/II criteria, revised Bethesda criteria).	EC		

3.3 Procedure on suspicion of a hereditary form of endometrial cancer

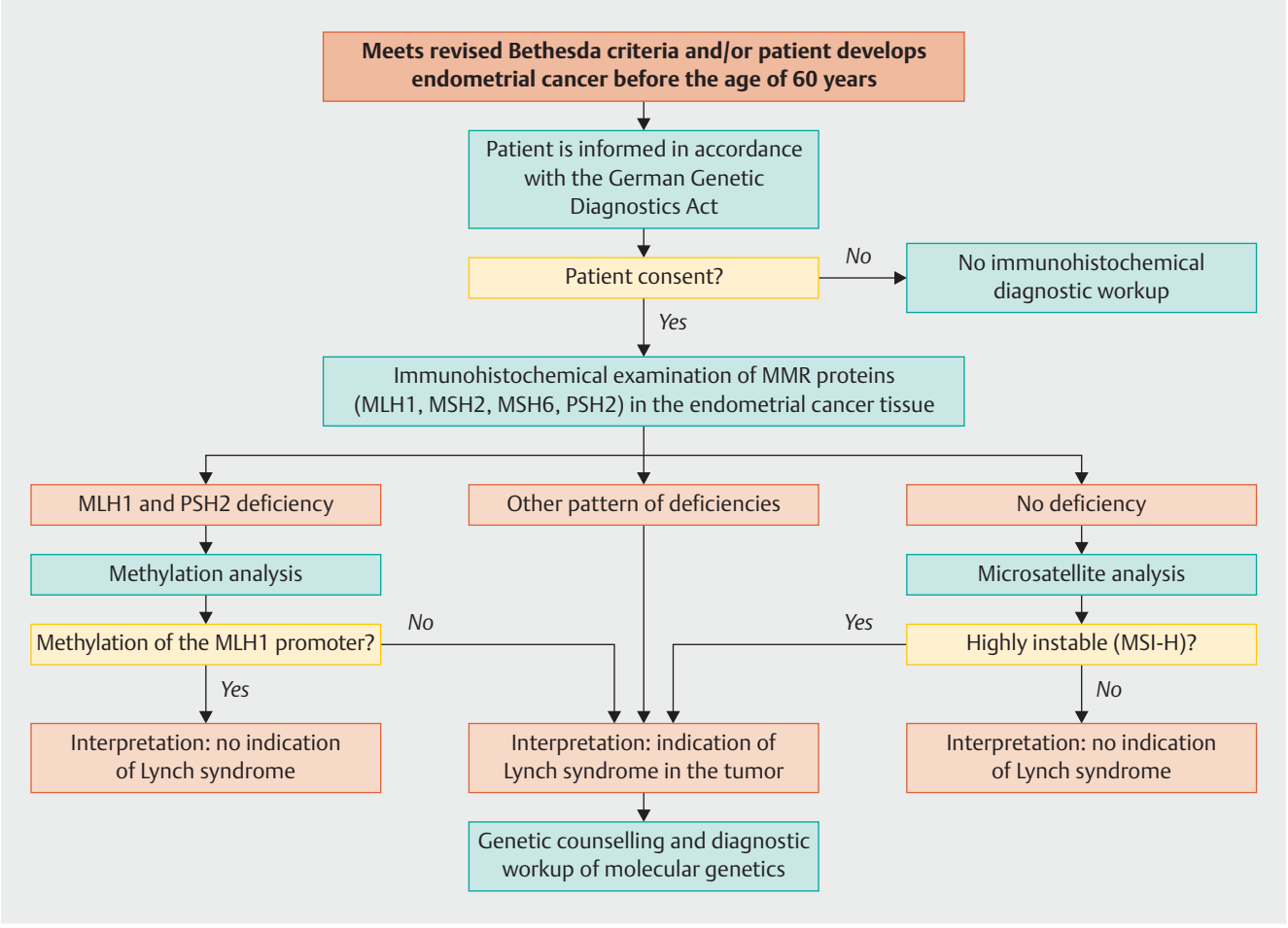
No.	Recommendation	GoR	LoE	Sources
10.3	If there is a suspicion that the patient has a hereditary form of endometrial cancer, the patient should be referred to a certified gynecological cancer center.	EC		

3.4 Psychosocial care

No.	Recommendation	GoR	LoE	Sources
10.4	Persons who have already developed disease, carriers, and people at risk for monogenic hereditary disease and an increased risk of developing endometrial cancer and other malignancies should be made aware of their options and the benefit of psychosocial counselling and care.	EC		

3.5 Clarifying clinically suspicious findings

No.	Recommendation	GoR	LoE	Sources
10.5	If at least one criterion of the revised Bethesda criteria has been met, the (molecular) pathology of the tumor tissue must be investigated further for changes typical for Lynch syndrome. This includes investigating the immunohistochemical expression of DNA mismatch repair proteins, microsatellite analysis and possibly the methylation of MLH1 promoters.	A	3	[84, 87 – 89, 100]
10.6	A (molecular-)pathological examination for Lynch syndrome in tumor tissue should be carried out in patients under the age of 60 in whom an endometrial carcinoma is diagnosed.	B	3	[84, 87 – 89, 100, 104]
10.6.1	It is still a matter of controversy whether these examinations of tumor material require medical information and counseling to be provided and consent to be given in accordance with the requirements of the law on genetic diagnosis. Until an authoritative interpretation of the gene diagnosis law relative to Lynch syndrome screening in endometrial carcinoma tumor material becomes available, the appropriate information and consent in accordance with the genetic diagnosis law should be ensured before the above molecular-pathological analyses of tumor material are carried out.	EC		
10.7	In patients from families in which the Amsterdam criteria are met, but whose tumor tissue does not show the abnormalities typical of Lynch syndrome, Lymph syndrome is not excluded. For further assessment and additional diagnosis if appropriate, genetic counseling should therefore be carried out.	EC		



▶ **Fig. 3** Diagnostic workup of tumor samples to investigate for Lynch syndrome [80]. [rerif]

3.6 Search for germline mutations

No.	Recommendation	GoR	LoE	Sources
10.8	If a patient has abnormal molecular pathology findings suspicous for Lynch syndrome, the patient must be offered the option of searching for germline mutations in the probably affected MMR gene(s).	A	3	[84, 87 – 89, 100]
10.8.1	If the clinical criteria for another hereditary tumor syndrome with a higher risk of developing endometrial cancer have been met, the search for mutations in the probably affected genes must be carried out directly.	EC		

3.7 Procedure when evidence of mutations is absent or uncertain

No.	Recommendation	GoR	LoE	Sources
10.9	If molecular genetic testing was unable to clearly identify a pathogenic germline mutation, this does not mean that the patient has no hereditary tumor syndrome.	EC		

3.8 Primary prevention for high-risk groups

No.	Recommendation	GoR	LoE	Sources
10.10	Due to the lack of any data for these special risk groups, no separate recommendations can be given regarding the benefits of dietary measures or chemoprevention for primary prevention in these groups compared to the normal population.	EC		

3.9 Procedure for persons at risk for Lynch or Cowden syndrome

No.	Recommendation	GoR	LoE	Sources
10.11	Individuals who are at risk for Lynch syndrome or Cowden syndrome must be recommended to receive human genetics counseling before the start of the recommended screening/early detection examinations.	EC		
10.12	As soon as the causative mutation in the family is known, the patient must be encouraged to inform potentially affected family members about their increased risk.	EC		
10.13	If tests have excluded a familial mutation in a person at risk, then the general cancer screening procedures apply.	EC		

3.10 Endometrial cancer screening in patients with Lynch or Cowden syndrome

No.	Recommendation	GoR	LoE	Sources
10.14	To date, there is no evidence that screening for the early detection of endometrial cancer offers longer survival to patients with LS and CS. The limited data do not permit any inferences to be made concerning recommendations for or against any specific screening tests for the early detection of endometrial cancer in patients with Lynch syndrome or Cowden syndrome.	ST	4	[57, 58, 71, 105, 106]

3.11 Syndrome-specific screening procedures for patients or high-risk carriers of Lynch or Cowden syndrome

No.	Recommendation	GoR	LoE	Sources
10.15	Due to the broad tumor spectrum, syndrome-specific screening procedures, particularly the option of having a colonoscopy, must be recommended to patients and high-risk persons with Lynch syndrome or Cowden syndrome. Detailed information is available in the respective guidelines.	EC		

3.12 Procedure for carriers of Lynch or Cowden syndrome

No.	Recommendation	GoR	LoE	Sources
10.16	The advantages and disadvantages of prophylactic hysterectomy – and bilateral adnexectomy as well if appropriate in Lynch syndrome patients – must be discussed with carriers of Lynch syndrome and Cowden syndrome starting at age 40, or 5 years before the earliest age at diagnosis in the family, particularly when a surgical intervention for a different indication is planned.	EC		

Conflict of Interest

For conflict of interests see guideline report: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Endometriumkarzinom/LL_Endometriumkarzinom_Leitlinienreport_1.0.pdf, last accessed on 13.08.2018.

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Guideline Program

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. Birgit Seelbach-Göbel
Universität Regensburg
Klinik für Geburtshilfe und Frauenheilkunde
St. Hedwig-Krankenhaus Barmherzige Brüder
Steinmetzstraße 1–3, DE-93049 Regensburg

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, 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])
Innrain 66A, AT-6020 Innsbruck
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-1180 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

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